Weight loss interventions in obese patients with chronic kidney disease

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Weight Loss Interventions in Obese Patients with Chronic Kidney Disease

A thesis submitted for the degree of Doctor of Philosophy

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Abstract

Observational studies suggest there is an independent relationship between obesity and chronic kidney disease (CKD). The mechanisms of this relationship remain unclear, although contributing factors include inflammation, insulin resistance, and hypertension. The aim of this thesis was to investigate the relationship between obesity and CKD using a range of study methodologies, deploying established and novel weight loss interventions.

Participation in a structured multidisciplinary weight loss intervention may be associated with a longer event-free period for the combined outcome of all cause mortality and cardiovascular morbidity in obese patients with CKD, compared to those referred to, but not participating in the intervention. Estimated kidney function significantly under-predicted measured glomerular filtration rate in obese patients with stages 3-4 CKD. Laparoscopic sleeve gastrectomy weight loss surgery was effective for weight loss in obese patients with CKD, although, in the small samples studied in this thesis, the risk for complications and adverse events, including mortality, may be greater in patients undergoing haemodialysis than in obese patients with earlier stages of CKD. Sleeve gastrectomy resulted in significantly greater weight loss than best medical care in obese patients with CKD, and may improve kidney function by reducing hyperfiltration. Quality of life, adiponectin and insulin resistance improved following sleeve gastrectomy, compared to best medical care in obese patients with moderate CKD. The odds ratio for CKD increases with overweight and obesity in the Health Survey for England 2010, compared to healthy weight participants. Evidence of a relationship between obesity and risk of CKD in a national sample of the United Kingdom population confirms the perceived need for safe and effective weight loss interventions for obese patients with CKD in a national context.

In summary, these results cautiously support the overarching hypothesis that weight loss is beneficial in obese patients with CKD, yet the risks of weight loss surgery in patients undergoing haemodialysis must be carefully considered against the perceived benefits. Further studies validating measures of kidney function in obese patients with CKD, and examining the safety and effectiveness of surgical and non-surgical weight loss interventions, are warranted.

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Abbreviations

ANOVA	analysis of variance
BMC	Best Medical Care treatment group in Ch 5 study
BMI	body mass index
CFU-Hill	Colony forming units cultured using the Hill assay
CI	confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated glomerular filtration rate, derived from various equations
EPC	Endothelial progenitor cells
GFR	Glomerular Filtration Rate
HADS	Hospital Anxiety and Depression Scale
HDL	high density lipoprotein fraction of serum cholesterol
HOMA-IR	Homeostatic Model of Assessment for Insulin Resistance
hs-CRP	high sensitivity C- reative protein
IBW	ideal body weight (body mass index = 25)
IL-6	interleukin-6
kcal	kilocalorie
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low density lipoprotein fraction of serum cholesterol
LSG	Laparoscopic Sleeve Gastrectomy treatment group in Ch 4 study
MDRD	Modification of Diet in Renal Disease study
MINAP	Myocardial Infarction National Audit Project
NKF-KDOQI	National Kidney Federation Kidney Disease Outcomes Quality Initiative
nSTEMI	non ST elevation myocardial infarction
OR	odds ratio
PBMC	peripheral blood mononuclear cells
PWV	pulse wave velocity
SF-36	Short Form 36 health survey
SG	Laparoscopic Sleeve Gastrectomy treatment group in Ch 5 study
TNF-α	Tumour necrosis factor alpha
UC	Usual Care treatment group in Ch 4 study
WHO	World Health Organisation
WMP	Weight Management Programme

Acknowledgements

First and foremost, I would like to thank my supervisor Dr Wendy Hall for her support, wisdom, clarity and much needed calmness in the often turbulent circumstances surrounding the execution of this body of work. I owe a debt of gratitude to Professor Iain Macdougall, for bravely going into battle for me on more occasions that thought possible. I'm sure neither of us would have embarked on this path had we known what lay before us, yet I'm grateful that we did. Professor Tom Sanders provided moments of clarity, and the motivation to be the best I could be.

I thank the members of the Renal Research Group at King's College London - Andi, Alex, Ayesha, Lucy, and Adam for their invaluable assistance and impromptu baby sitting, and Maz for guiding me through the lab and teaching me the basics of cell culture. I'd also like to thank the Renal Exercise and Nutrition Team at King's College Hospital; especially Sharlene Greenwood for not only practical and moral support, but for understanding everything, and Rochelle Blacklock, for her assistance with data collection, and Deepa, Rochelle and Helen for carrying on the clinical service so exceptionally.

This thesis is dedicated to my family; first and foremost to my husband, Anthony, as without his unerring support, kindness and often far stretched capacity to give, this work would not have been possible. I also owe this dedication to our boys, Flynn and Felix, who have sacrificed more than they will ever know, and I can only hope to make it up to them when it becomes their turn.

I would also like the thank the King's College Hospital Research and Development Department and the British Renal Association for providing the means to fund this work.

Publications, Conference Presentations and Prizes

Publications related to this thesis

MacLaughlin HL, Greenwood SA. Weight management for obese patients on the renal ward. J Ren Nursing 2010; 2: 116-121.

MacLaughlin HL, Hall WL, Patel AG, Macdougall IC. Laparoscopic sleeve gastrectomy is a novel and effective treatment for obesity in patients with CKD. Obes Surg 2012; 22: 119-23.

MacLaughlin HL, Hall WL, Patel AG, Blacklock RM, Macdougall IC. Kidney Function, Adipokines, and Quality of Life after Weight Loss Surgery in Obese Patients with Stages 3-4 Chronic Kidney Disease: A Randomized Controlled Pilot Study [Abstract]. J Am Soc Nephrol 24, 2013: 543A.

MacLaughlin HL, Hall WL, Macdougall IC. Obesity as a Risk Factor for Chronic Kidney Disease: Health Survey for England 2010 [Abstract]. J Am Soc Nephrol 24, 2013: 669A.

Conference presentation related to this thesis

MacLaughlin HL, Greenwood, SA, Hall WL, Sanders TAB, Macdougall IC. Participation in a structured weight loss program improves survival in obese patients with CKD. International Congress of Dietetics 2012, Sydney, Australia (selected for oral presentation).

MacLaughlin HL, Macdougall IC, Ahmed AR, Patel AG, Chang A, Burns A, Finer N, Chahal H, Tharakan G, Pucci A, Tam FWK, Johansson L, Flint J, Frankel AH. Safety and efficacy of bariatric surgery in obese patients with CKD: the London Renal Obesity Network (LonRON) experience. American Society of Nephrology Kidney Week 2013, Atlanta, USA (selected for oral presentation).

Other publications by the candidate during the PhD study period

MacLaughlin HL, Cook SA, Kariyawasam D, Roseke M, van Niekerk M, Macdougall IC. Nonrandomized Trial of Weight Loss with Orlistat, Nutrition Education, Diet, and Exercise in Obese Patients with CKD: 2-Year Follow-up. Am J Kidney Dis 2010; 55: 69-76.

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Prizes

School of Medicine Graduate Research Showcase King's College London 2012 Best Poster Prize

British Dietetic Association General Education Trust Travel Bursary 2012

Preamble

This thesis explores weight loss interventions in obese patients with chronic kidney disease. The studies reported in this thesis address specific research aims designed to explore different weight loss methods and to study the effect of weight loss interventions on specific outcomes including kidney function, survival, and quality of life, and to establish whether a relationship is apparent between obesity and the prevalence of chronic kidney disease in the United Kingdom. The studies are exploratory in nature, and set out to establish the safety and effectiveness of weight loss interventions in obese patients with chronic kidney disease. This thesis does not set out to establish the mechanisms of the effect of weight loss on kidney function or cardiovascular risk factors in this population.

Thesis aim

The overarching purpose of this thesis was to examine the relationship between obesity and chronic kidney disease using a range of study methodologies. This broad approach included a retrospective observational study to examine of the effect of participation in a structured lifestyle weight loss intervention on morbidity and mortality outcomes. An in-depth exploration of a surgical weight loss technique, the laparoscopic sleeve gastrectomy, reported for the first time in obese patients with chronic kidney disease, encompassed three studies, a case series, an observational cohort study and a randomised controlled pilot study. Finally, an epidemiological approach was used to determine the risk of chronic kidney disease with obesity in two large United Kingdom population databases, to establish the extent of the problem in a national context.

Thesis structure

Each study is presented in complete form as a distinct chapter, with the introduction to the topic preceding the studies and the concluding discussion culminating in an in-depth examination of the implications of the research findings, with a forward projection focussing on future studies.

The structure of the thesis is as follows:

Chapter 1: Introduction

This chapter considers the literature on the relationship between obesity and chronic kidney disease. In particular, how obesity contributes to the development of chronic kidney disease is examined, and the effect of weight loss interventions on delaying or preventing progression of chronic kidney disease or improving other patient focused outcomes is explored, with the aim of identifying significant gaps in the evidence and to inform the subsequent study designs featured in this thesis.

Chapter 2: Participation in a structured weight loss programme and all-cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease

This study describes the participants and non-participants who self-selected to attend, or not attend, a structured, multidisciplinary weight management programme and aims to determine if participation in a weight loss programme impacts upon all-cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease, over up to 6 years of follow up.

Chapter 3: Laparoscopic sleeve gastrectomy - a novel technique for weight loss in obese patients with chronic kidney disease

This study describes the first case-series of obese patients with chronic kidney disease undergoing sleeve gastrectomy, performed in a single centre in the United Kingdom. The study reports on the extent of weight loss achieved, and documents the surgical complications and post-operative adverse events over the observation period.

Chapter 4: A prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in obese patients on haemodialysis - pilot study

This study aims to evaluate the effectiveness of the sleeve gastrectomy procedure to elicit sufficient weight loss to enable kidney transplantation in obese patients with kidney failure currently undergoing haemodialysis. Additionally, the effectiveness of the procedure for improving quality of life, reducing insulin resistance, hypertension and dyslipidaemia was studied, and adverse effects were monitored.

Chapter 5: The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with chronic kidney disease: a randomised controlled pilot study

This randomised controlled parallel-design pilot study aims to evaluate the effect of weight loss surgery on kidney function, compared to best medical treatment, including a structured multidisciplinary weight management programme, in obese patients with chronic kidney disease. Additionally the effects of the two different weight loss treatments on adipocytokines and quality of life will be examined in this patient population.

Chapter 6: Prevalence of Chronic Kidney Disease by Body Mass Index in the Health Survey for England and in Patients with Acute Coronary Syndromes in England and Wales

This study aims to determine if the relationship evident between body mass index and prevalence of chronic kidney disease in European and North American populations is also apparent in two United Kingdom populations: the Health Survey for England 2010 randomly sampled population, and the Myocardial Infarction National Audit Project (MINAP) selectively sampled population with existing cardiovascular disease.

Chapter 7: Discussion

The final chapter presents a summary of the findings of the 5 studies included in this thesis and discusses some of the strengths and weakness of the different weight loss intervention methodologies explored in this body of work. A detailed discussion is presented on developing future studies of weight loss surgery interventions in obese patients with chronic kidney disease, using a structured framework for research in surgical innovation.

Chapter 1: Introduction

Chronic kidney disease (CKD) is becoming increasingly prolific, and now significantly contributes to the national and global burden of disease, affecting nearly 1 in 10 adults in the United States and 1 in 20 in the United Kingdom (UK) (Coresh, Astor et al. 2003; John, Webb et al. 2004; Schoolwerth, Engelgau et al. 2006). CKD is defined as structural or functional abnormalities of the kidney, present for at least 3 months, which impact upon health (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). The following chapter will explain how kidney function is defined and measured, introduce the definition and classification of the stages of CKD, and consider the literature on the relationship between obesity and CKD, in particular, how obesity contributes to the development of CKD, and the effect of weight loss interventions on delaying or preventing progression of CKD or improving other patient focused outcomes, with the aim of identifying significant gaps in the evidence and to inform the subsequent study designs featured in this thesis.

Role of the kidney and glomerular filtration rate

The role of the kidney is to retain adequate fluid, protein, electrolytes and hormones for optimal body function and facilitate the excretion of the excess, including the by-products of protein metabolism, urea and creatinine, by filtering the blood through the glomeruli. Regardless of the cause, as kidney function declines with a reduction in the glomerular filtration rate (GFR), or kidney filtration capacity, the ability to perform these functions is progressively reduced and the urea and creatinine, plus other substances, accumulate in the plasma, and proteins that are normally retained for re-use in the body, may be excreted in urine (Mitch and Klahr 2005).

GFR is measured by determining the rate of clearance, in millilitres per minute (ml/min), of a exogenous marker that meets the requirements of an ideal filtration substance (Gaspari, Perico et al. 1995). The substance must be freely filtered by the glomeruli and not taken up by the renal tubules, must not be made or broken down by the body and should be physiologically inert (Gaspari, Perico et al. 1995). Classically, inulin, a fructose polymer, has been the gold standard marker for measurement of GFR, but it requires a continuous intravenous infusion of inulin and patients must be bed rested (Gaspari, Perico et al. 1995). Therefore, other endogenous markers that can be administered with a single injection, such as radioactive [^{51}Cr] ethylene diamine tetraacetic acid (EDTA), or the non-ionic, low-osmolar radiological contrast medium, iohexol, have been studied and are now considered to be highly correlated to inulin clearance (Gaspari, Perico et al. 1995; Brandstrom, Grzegorczyk et al. 1998). Clinically, even iohexol measured GFR is difficult to implement into practice, due to the time and expertise required to measure it, and estimations of GFR, based on serum creatinine levels, are typically calculated. Presently, the most common prediction equation for estimated GFR (eGFR) is the 4-variable Modification in Diet and Renal Disease study equation, which requires serum creatinine, sex, age and ethnicity, and correlates well with measured GFR when kidney function is impaired, but is less representative of GFR when kidney function is normal (Levey, Bosch et al. 1999; Levey, Greene et al. 2000). More recently, the CKD Epidemiology Collaboration (CKD-EPI) have addressed this issue, with the development and validation of the CKD-EPI equation to estimate GFR, however, this estimation equation is not yet in widespread use, as validation studies in broader population groups, are still being carried out (Levey, Stevens et al. 2009; Matsushita, Mahmoodi et al. 2012).

Definition of Chronic Kidney Disease (CKD)

CKD is defined by both degree of damage and time. Structural or functional kidney damage must be evident on at least 2 occasions over a period of at least 3 months, and is further classified into 5 stages by the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) (Levey, Coresh et al. 2003). Table 1 lists the stages from mild disease at stage 1 with kidney damage (proteinuria, haematuria or an anatomical abnormality) and normal kidney function to the most severe form at stage 5, in which kidney function is less than 15% of normal level and/or life-saving renal replacement therapy such as dialysis or kidney transplantation is required (Levey, Coresh et al. 2003).

Table 1: NKF-KDOQI stages of chronic kidney disease (adapted from Levey, Coresh et al 2003)

Stage	Description	Glomerular Filtration Rate (GFR) (ml/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure	<15 (or dialysis)

Kidney function is predictive of mortality in the general population, with risk increasing once eGFR falls below 60 ml/minute with even trace amounts of albuminuria (Chronic Kidney Disease Prognosis Consortium, 2010). These classifications are based on eGFR measurement, which is most often used in practice to identify the stage of CKD, and monitor kidney disease progression.

In patients with kidney failure requiring dialysis, 50% of the mortality is due to cardiovascular causes, with the risk of death from a cardiovascular cause, on average, 15-30 times higher than the age-adjusted mortality in the general population (Schiffrin, Lipman et al. 2007), and 500 times higher in young patients aged 25-34 years (Sarnak, Levey et al. 2003) . This relationship is also evident in earlier stages of CKD, with a 3 fold greater adjusted hazard ratio for the risk of all cause mortality and cardiovascular morbidity in those with impaired kidney function compared to those with normal kidney function, after adjustment for age, sex, race, socio-economic status and co-existing illness (Go, Chertow et al. 2004).

Three recent meta-analyses examined the additional effect of age, hypertension or diabetes on the relationship between eGFR and mortality, and found that whilst diabetes and age were associated with increased absolute mortality risk across the ranges of eGFR, neither age, nor diabetes, or hypertension increased the relative risk for mortality for any given level of eGFR (Fox, Matsushita et al. 2012; Hallan, Matsushita et al. 2012; Mahmoodi, Matsushita et al. 2012). These findings indicate that eGFR is a stronger predictor of outcome, and points towards aggressive management of all cardiovascular risk factors, such as glycaemic control, lipids, and obesity in all patients with, or at risk of developing, CKD.

Prevention of progression of CKD

Over the last 10 years, emphasis has been placed on the implementation of national secondary prevention measures to prevent the progression of CKD in the United Kingdom. These measures include the expansion of the National Renal Service Framework to include identification and management of CKD prior to end stage disease, improved detection of CKD, and the inclusion of renal indicators within the Quality

Outcomes Framework incentive scheme for General Practitioners (The Health and Social Care Information Centre 2009) .

The second stage of the National Renal Service Framework (Figure 1), published by the Department of Health in 2005, contains two key quality requirements pertaining to screening, assessment and management of CKD (Department of Health 2005).

Quality requirement 1 – "People at increased risk of developing or having undiagnosed CKD, especially people with diabetes or hypertension, are identified, assessed, and their condition managed to preserve their kidney function."

Quality requirement 2 – "People with a diagnosis of CKD receive timely, appropriate and effective investigation, treatment and follow-up to reduce risk of progression and complications."

Figure 1: Renal National Service Framework quality requirements relating to prevention of CKD (Department of Health 2005)

In 2006, reporting of estimated GFR (eGFR) – an estimate of kidney function – was incorporated into standard biochemistry practice, which led to increases in the known prevalence of CKD and referral of patients with CKD to specialist services in the United Kingdom (Zoccali, Kramer et al. 2009). Additionally, the NHS Quality Outcomes Framework for General Practice recognises the importance of screening and management of CKD, with the introduction of CKD indicators in 2006/2007, and most Practices now hold a CKD register (The Health and Social Care Information Centre 2009). Furthermore, National Institute of Health and Clinical Excellence (NICE) guidelines for the identification, management and referral of adults with CKD were produced in 2008 (National Institute for Health and Clinical Excellence 2008). These guidelines recommend targeting of patients with CKD risk factors, such as hypertension, diabetes, cardiovascular disease, or a family history of kidney failure for CKD screening and optimising treatment. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group have just

published an internationally agreed clinical practice guideline for the evaluation and management of CKD, which recommend addressing risk factors to improve cardiovascular health, including blood pressure (BP), blood sugar, dyslipidaemia, exercise and achieving a healthy weight (body mass index (BMI) 20-25 kg/m^2, according to country specific demographics) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013).

This strategic emphasis on the prevention, and management of CKD and its associated risk factors highlights the enormity of the consequences of failing to halt progression of CKD towards end stage kidney disease. These strategies share a common theme of focusing on the detection and management of CKD and its most common contributing aetiologies, diabetes and hypertension, to ensure that patients diagnosed with CKD receive treatment and long term follow up to reduce the risk of progression of CKD, which is associated, not only with high economic cost, but also increased mortality.

Early and aggressive treatment of the major risk factors, such as hypertension, proteinuria and diabetes, may prevent progression of CKD to end stage kidney failure (Hallan, Coresh et al. 2006). Intensive treatment of patients with type 1 diabetes to elicit near-normal glycaemic control in resulted in a reduction in the long-term risk of the development of CKD (de Boer, Sun et al. 2011). Patients enrolled in the study had type 1 diabetes for 1-5 years plus no, or very mild, microvascular complications at baseline. The reduction in incidence of CKD was attenuated by glycaemic control and albuminuria, indicating that it is via these mechanisms that intensive treatment of diabetes can reduce the risk of the development of CKD. Similarly, incident patients with type 2 diabetes randomised to intensive glycaemic control in the United Kingdom Prospective Diabetes Study experienced a 24% lower relative risk of developing microvascular complications (which

included CKD) after 10 years, however, there was no protective effect in overweight patients (Holman, Paul et al. 2008).

Recent evidence from the 4th National Health and Nutrition Examination Survey (NHANES IV) suggests that the rising prevalence of obesity is an additional contributing factor to early kidney damage (Coresh, Selvin et al. 2007), although evidence of a causal link is lacking. A systematic review and meta-analysis in 2008 demonstrated a 4-fold increased risk of end-stage kidney failure with obesity (Wang, Chen et al. 2008) and population studies have also established an association between obesity and prevalent CKD (Kramer, Luke et al. 2005; Hallan, de Mutsert et al. 2006; Burton, Gray et al. 2012). Nutritional treatment remains the cornerstone of obesity management when using both lifestyle and surgical interventions. Current practice guidelines for nutritional intervention in CKD (2000; Fouque, Vennegoor et al. 2007; Renal Association 2007) provide very little guidance on the management of obesity in patients with CKD, and the majority of evidence is gleaned from epidemiological studies rather than clinical intervention trials.

Further research on the contribution of obesity to the development and progression of CKD may provide additional information upon which to base future preventative strategies targeting treatment of obesity alongside diabetes and hypertension, to reduce the societal burden of CKD.

Chronic Kidney Disease and Cardiovascular Disease Risk

Patients with CKD are more likely to die of cardiovascular causes than reach end stage kidney disease, and cardiovascular disease accounts for one-third of deaths in haemodialysis patients in the United Kingdom (Shulman, Ford et al. 1989; Ansell 2008). A systematic review of 85 studies and over 550 000 patients provides strong evidence that

CKD is associated with cardiovascular risk from an early stage and the risk increases progressively with declining kidney function (Vanholder, Massy et al. 2005). As traditional risk factors for cardiovascular disease, such as diabetes and hypertension, are also common causes of kidney disease, the relationship between CKD and cardiovascular disease is likely to be bidirectional, and early stage CKD may be a marker of cardiovascular damage (Stenvinkel, Carrero et al. 2008). The presence of hypertension, diabetes and hyperlipidaemia, all worsened in the presence of CKD, may lead to endothelial dysfunction, causing changes to the media of blood vessel walls resulting in thickening and reduced vascular elasticity (Schiffrin, Lipman et al. 2007), which is an early phase of atherosclerosis (Dogra, Irish et al. 2006). However, the mortality rate due to cardiovascular causes in haemodialysis patients is higher than can be accounted for due to these traditional cardiovascular risk factors alone (Stenvinkel, Carrero et al. 2008), indicating that other parallel processes are also contributing to the increased cardiovascular disease risk.

Hypertension and cardiovascular disease are associated not only with lifestyle risk factors but also with low birth weight; a relationship first proposed by Barker, based on research conducted in the 1980s and 1990s (Barker 1990; Barker, Bull et al. 1990). Low birth weight is also associated with reduced nephron number and increased prevalence of albuminuria, a manifestation of hyperfiltration (an absolute increase in glomerular filtration rate (Helal, Fick-Brosnahan et al. 2012)), which leads to glomerular damage (Brenner, Garcia et al. 1988; Hoy, Rees et al. 1999). Whilst it is tempting to conclude that low birth weight may be directly associated with the development of CKD, there remains a lack of direct evidence supporting a link between reduced nephron number, glomerular hyperfiltration and an increased risk of the development of CKD (Schreuder and Nauta 2007), and the relationship may be mediated by a concurrent process with diabetes or cardiovascular disease (Zandi-Nejad, Luyckx et al. 2006; Franco, Oliveira et al. 2012).

Reduced kidney function causes changes in endothelial structure and function that may trigger the inflammatory response evident in CKD (Schiffrin, Lipman et al. 2007), which is associated with mortality in haemodialysis patients (Pecoits-Filho, Barany et al. 2002). Populations of endothelial progenitor cells (EPC), which are bone marrow derived circulating progenitor cells required for regeneration and repair of injured and inflamed endothelium (Hill, Zalos et al. 2003; Muller-Ehmsen, Braun et al. 2008), are reduced in patients with CKD (Bahlmann, Speer et al. 2010), possibly due to uraemic toxicity (de Groot, Bahlmann et al. 2004). Measurement of circulating EPC is performed with either flow cytometry to count the number of cells, or by culturing cells into colonies, which provide a functional measure of EPC capacity to assist in vascular repair and regeneration, and both indices of EPC correlate inversely with cardiovascular risk in those without CKD (Hill, Zalos et al. 2003; Maruyama, Taguchi et al. 2008; Lorenzen, David et al. 2010). In haemodialysis patients, a reduction in the number of active EPC was associated with cardiovascular events, but did not correlate with traditional cardiovascular risk factors such as hypertension and hypercholesterolaemia, indicating that the reduction in repair and regeneration capacity brought about by the reduction in EPC may play a role in the increased cardiovascular disease risk in this population group (Lorenzen, David et al. 2010).

Other contributing factors to endothelial dysfunction in patients with CKD include insulin resistance (Shinohara, Shoji et al. 2002), increased activation of the renin-angiotensin system, increased oxidative stress, and impaired bone mineral metabolism (Schiffrin, Lipman et al. 2007). In a cross sectional study of patients with stages 3-5 CKD and healthy age, gender, and BMI matched control healthy subjects, exploring the effect of both novel and traditional cardiovascular risk factors on vascular dysfunction, patients with stages 3-5 CKD had higher waist circumference, systolic blood pressure, insulin resistance, triglycerides and raised makers of inflammation, compared to healthy controls (Dogra,

Irish et al. 2006). Insulin resistance is related to cardiovascular mortality but not all cause mortality in end stage kidney disease patients, independently of BMI, hypertension and dyslipidaemia (Shinohara, Shoji et al. 2002), indicating that insulin resistance may cause vascular damage via a pathway not directly associated with the atherosclerotic processes associated with traditional cardiovascular risk factors.

Insulin resistance, measured by the Homeostasis Method Assessment of Insulin Resistance (HOMA-IR) (Matthews, Hosker et al. 1985) - a valid measure of insulin resistance in patients with CKD (Shoji, Emoto et al. 2001) - was associated with CKD in a sub-analysis of the 3rd National Health and Nutrition Examination Survey (Chen, Muntner et al. 2003). The relationship was maintained after adjustment for multiple confounders, and this was the first study to demonstrate a link between insulin resistance and CKD in a population without diabetes. Furthermore, in a prospective study of over 10 000 subjects without diabetes or CKD at baseline, the odds ratio of developing CKD after 9 years of follow up was 1.7 (95% CI 1.26 to 2.30) for the highest quintile of insulin resistance, compared to the lowest (Kurella, Lo et al. 2005). Insulin resistance is known to be associated with albuminuria (a risk factor for both cardiovascular disease and CKD), which occurs due to increased permeability of the glomerular filtration membrane via structural damage to the intricate foot processes of the podocytes, possibly through several mechanisms including a deficiency of insulin receptors on the podocyte, regulation by adipose tissue cytokines, and activation of the renin-angiotensin-aldosterone system (Fornoni 2010; Kalaitzidis and Siamopoulos 2011; Nistala and Whaley-Connell 2013).

The inflammation, insulin resistance, and hypertension associated with both obesity and CKD result in changes to the structural organisation of collagen and elastin, which determine the stiffness of the arterial wall, and to the haemodynamics of blood flow due to

increased pressure (Laurent, Cockcroft et al. 2006). Arterial stiffness can be measured directly, and non-invasively, using the gold standard method of carotid to femoral pulse wave velocity measurement, by dividing the distance the pulse wave travels by the time taken (Boutouyrie, Briet et al. 2009). Pulse wave velocity has been demonstrated to be predictive of cardiovascular events in patients with CKD. In a prospective observational study of 317 patients followed up for 3.6 years, pulse wave velocity was an independent predictor of combined fatal and non fatal cardiovascular events in patients with stages 4-5 CKD, and remained so after adjustment for established cardiovascular risk factors - age, gender, blood pressure, diabetes, past cardiovascular disease, cholesterol level, and smoking (Zoungas, Cameron et al. 2007). Reductions in arterial stiffness with therapeutic interventions represent a true reduction in arterial wall damage, rather than simply a change in cardiovascular risk scores achieved with reductions in hypertension, lipid lowering and improvement in glycaemic control (Laurent, Cockcroft et al. 2006). In haemodialysis patients, a reduction in arterial stiffness achieved through blood pressure control independently predicted a reduction in mortality, whereas a reduction in blood pressure, without a concomitant improvement in arterial stiffness, was related to increased mortality (Guerin, Blacher et al. 2001). These findings indicate that vascular remodelling, or a capacity for vascular remodelling, rather than a reduction in blood pressure per se, impact upon mortality and can reduce cardiovascular risk in the end stage kidney disease population.

In summary, both traditional cardiovascular risk factors, such as hypertension and hypercholesterolaemia, and non-traditional risk factors, including insulin resistance, inflammation, elevated waist circumference, increased vascular stiffness, and a reduction in the number and/or function of EPC contribute to the elevated cardiovascular risk evident in patients with CKD.

Role of obesity in the development and progression of CKD

Overweight and obesity may be best defined as an excess of adipose tissue in the body that may impair health. However, for both individuals and populations, body weight, classified with reference to height, using the body mass index (BMI; weight in kg/height in $(m)^2$) is used to classify obesity, largely due to its ease of measurement, and close association with adiposity in population studies. Overweight is a BMI $\geq$ 25kg/m^2 and obesity is classified as a BMI $\geq$ 30 kg/m^2 (World Health Organisation 2006). The prevalence of obesity, measured by BMI, has reached epidemic proportions across the developed and developing world, and it is rapidly becoming a greater public health problem than malnutrition or infectious diseases (World Health Organisation 1997).

The prevalence of CKD is increasing worldwide (Zhang and Rothenbacher 2008; Zoccali, Kramer et al. 2009), and hypertension and diabetes are well established precursors to the development of CKD (Cooper, Rotimi et al. 1997; Kearney, Whelton et al. 2004; Gonzalez, Johansson et al. 2009). In observational studies, obesity has been identified as an independent risk factor for the development of CKD and progression to kidney failure (Fox, Larson et al. 2004; Kramer, Luke et al. 2005; Munkhaugen, Lydersen et al. 2009; Othman, Kawar et al. 2009; Rossi, Nicolucci et al. 2010), and remains so, after adjustment for hypertension and diabetes in some studies (Gelber, Kurth et al. 2005; Hallan, de Mutsert et al. 2006; Hsu, McCulloch et al. 2006; Kawamoto, Kohara et al. 2008; Satirapoj, Supasyndh et al. 2012), but not all (Foster, Hwang et al. 2008). Evidence relating to obesity as a risk factor for the progression of earlier stages of CKD is equivocal (Othman, Kawar et al. 2009; Brown, Mohsen et al. 2012; Mohsen, Brown et al. 2012), and differences may relate to the number of repeated measures of kidney function, the length of follow up and the inaccuracy of indexed estimated measures of kidney function in obesity, particularly over time (Delanaye, Radermecker et al. 2005; Chang and Kramer 2012).

In a large population based cross-sectional study of over 65 000 Norwegian men and women enrolled in the Health Survey of Nord-Trondelag County (HUNT II), the relationships between CKD, defined as an eGFR < 45 ml/min/1.73m^2 using the MDRD equation, and obesity, physical inactivity and smoking were studied (Hallan, de Mutsert et al. 2006). After adjustment for age and sex, the relative risk of CKD with a BMI ≥ 30 kg/m^2 was 1.77 (95% CI 1.47-2.14). Obesity remained an independent risk factor for CKD after further adjustment for diabetes, hypertension, blood lipids and cardiovascular disease (adjusted relative risk 1.44, 95% CI 1.18-1.75). The results of this study are supported by a smaller, more recent study in a Japanese community based population, with the risk of CKD, defined as eGFR<60 ml/min/1.73m^2 using the MDRD equation, doubling with overweight and obesity, after multivariable adjustment (Kawamoto, Kohara et al. 2008).

Furthermore, the relationship between obesity and CKD is also evident in patients with known hypertension. The prevalence of CKD increased with obesity at baseline in the Hypertension Detection and Follow Up Program patient population, and in patients without CKD at baseline the risk of developing CKD after 5 years increased with increasing BMI (Kramer, Luke et al. 2005). In 9 585 patients with hypertension (diastolic BP > 90 mm Hg) at baseline, the prevalence of CKD, again defined as eGFR <60 ml/min/1.73m^2 using the MDRD equation, was 18% in the normal BMI group and 22% in the obese group (p <0.001). Using logistic regression modelling, after adjustment for age, sex and race, the risk of CKD with BMI ≥ 30 kg/m^2 was increased (odds ratio 1.32, 95% CI 1.15 – 1.54). The relationship remained statistically significant after further adjustment for diabetes and blood pressure (OR 1.23, 95% CI 1.07 – 1.40) (Kramer, Luke et al. 2005). The authors went on to explore the development of incident CKD in 5 897 hypertensive patients without evidence of CKD at baseline. After 5 years, the OR of

developing CKD in patients with a baseline BMI of ≥ 30 kg/m^2 was 1.40 (95% CI 1.20 – 1.63), after adjustment for age, sex, race, diabetes and hypertension variables. The risk of developing CKD after 5 years was also increased in overweight patients in this study, demonstrating a link between increasing BMI and the development of CKD after controlling for established risk factors including diabetes and hypertension (Kramer, Luke et al. 2005).

Two further longitudinal studies, in apparently healthy cohorts at baseline, also studied the development of CKD with increasing BMI. Using information collected in the Physicians' Health Study, in 11 000 men with a mean follow up period of 14 years, the risk of developing CKD, defined as an eGFR <60ml/min using the MDRD study equation, was increased (OR 1.45, 95% CI 1.19-1.76), in the highest BMI quintile (BMI > 26.6 kg/m^2), compared with lowest BMI quintile (< 22.7 kg/m^2) after adjustment for age, smoking, alcohol, exercise and parenteral history of myocardial infarction at < 60 years of age. Further adjustment for diabetes, cardiovascular disease, hypertension and cholesterol, attenuated the relationship, but it remained significant (adjusted OR 1.26, 95% CI 1.03 – 1.54) (Gelber, Kurth et al. 2005). This increased risk of developing CKD was also evident in obese participants in the Framingham Offspring Study cohort (Fox, Larson et al. 2004), but became non-significant after adjustment for diabetes, hypertension, smoking status and baseline HDL-cholesterol (adjusted OR 1.09, 95% CI 0.69 – 1.73) (Foster, Hwang et al. 2008).

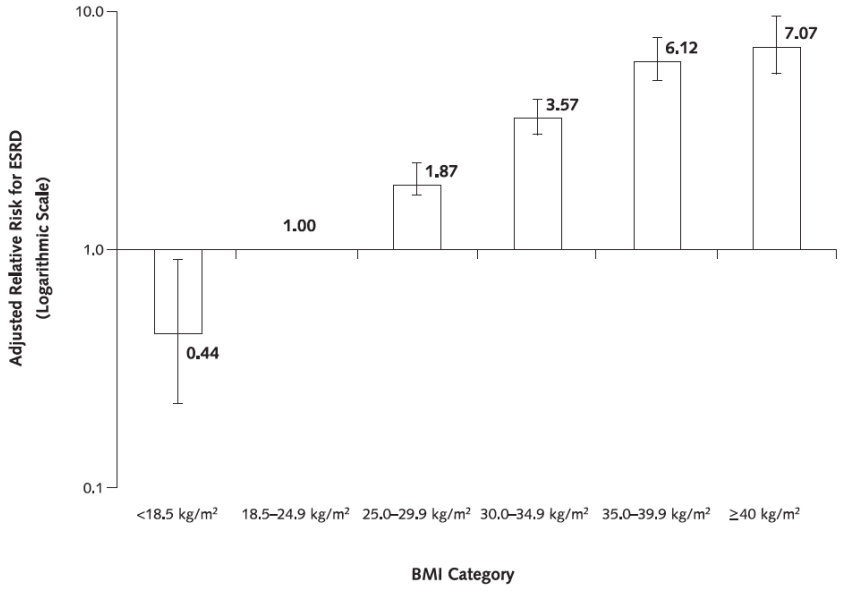
In a recent study examining the relationship between baseline BMI and progression of CKD over at least 5 years in 125 patients without diabetes, younger age and greater baseline BMI predicted worsening of kidney function ($R^2 = 0.12$, $p < 0.001$), whilst blood pressure and proteinuria did not (Othman, Kawar et al. 2009). Obese patients also had

higher follow-up blood pressure and triglycerides than normal weight patients, both of which are known modifiable CKD risk factors (National Institute for Health and Clinical Excellence 2008).

Metabolic syndrome is defined by the National Cholesterol Education Program (NCEP) Revised Adult Treatment Panel (ATP) III criteria as the presence of at least 3 of the following metabolic disturbances: hypertension, impaired glucose metabolism, dyslipidaemia and abdominal obesity, and contributes to cardiovascular disease risk (Grundy, Cleeman et al. 2005). Some, or all, of the key elements of metabolic syndrome are evident in patients with CKD (Ross and McGill 2006), and metabolic syndrome has also been identified as a precursor to CKD in a large cross sectional study of over 6 000 adults (Chen, Muntner et al. 2004). A recent meta-analysis of prospective cohort studies examined the relationship between metabolic syndrome, its components, and development of CKD (eGFR < 60 ml/min/1.73m^2) (Thomas, Sehgal et al. 2011). Fully adjusted risk estimates were pooled for the 10 studies meeting the inclusion criteria. The pooled OR for the development of CKD in patients with metabolic syndrome was 1.55 (95% CI 1.34 – 1.80) with mean follow up of 5.8 years (Thomas, Sehgal et al. 2011). Furthermore, the impact of each of the individual components of metabolic syndrome on the development of CKD was evaluated, and the OR of CKD with obesity was 1.19 (95% CI 1.05 – 1.34), which is a similar level of risk evident in other studies examining this relationship (Gelber, Kurth et al. 2005; Kramer, Luke et al. 2005; Othman, Kawar et al. 2009).

There is strong evidence for a relationship between obesity and the development of end stage kidney disease in 2 large longitudinal studies. This relationship was first evident in an analysis of over 320 000 health screening records in the Kaiser Permanente Health System database, against the United States Renal Data System records for patients commencing

haemodialysis, peritoneal dialysis or undergoing kidney transplantation (Hsu, McCulloch et al. 2006). 1 471 cases of end stage kidney disease occurred in the 15-35 year follow-up period. The risk for the development of end stage kidney disease increased incrementally with increasing BMI over 25 kg/m^2 (Figure 2), after adjustment for baseline age, race, sex, education, smoking status, previous myocardial infarction, proteinuria, blood lipids, haematuria and serum creatinine.



Model adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Error bars represent 95% CIs.

Figure 2: Increasing risk of end stage kidney disease by BMI category (Hsu, McCulloch et al. 2006)

These results were supported by a more recent longitudinal study of the HUNT participants in Norway. After 21 years of follow up of almost 75 000 participants, participants with a baseline BMI of 30 kg/m^2 had a greater combined risk of CKD related death or commencing renal replacement therapy, and the effect remained after adjustment for sex, age, physical activity, smoking status, socioeconomic status, diabetes, cardiovascular disease and hypertension (Munkhaugen, Lydersen et al. 2009). The risk increased markedly in patients with blood pressure greater than 120/80 mm Hg, and the interaction of the 2 risk factors indicated that the effect of elevated blood pressure

combined with elevated BMI exerted an effect almost 6 times greater than that expected based on the addition of the 2 risk factors (Munkhaugen, Lydersen et al. 2009).

These studies demonstrate an independent relationship between obesity and the development of both moderate CKD and end stage kidney failure. In moderate CKD the risk is attenuated by other known CKD risk factors, indicating that whilst obesity does increase the risk of CKD development and progression, the relationship is multifactorial and there are likely to be several mechanisms associated with the reduction in kidney function evident over time with the increased metabolic demands of the obese state, commonly evident as a cluster of risk factors in metabolic syndrome. However, the level of increased risk is much higher for end stage kidney failure, than for moderate CKD, which may possibly be related to the longer follow up period in these studies, particularly if obesity related kidney disease manifests slowly. Understanding the mechanisms linking obesity and CKD is important, considering the concomitant rise in both obesity and CKD prevalence, to generate insights that may lead to potential therapeutic strategies to treat or prevent CKD and its associated co-morbidities (Ix and Sharma 2010).

Mechanisms of obesity related kidney damage

Obesity is associated with CKD progression and kidney failure, and whilst the exact mechanisms remain unknown, inflammation, dyslipidaemia, insulin resistance, and hypertension contribute to obesity related kidney damage (Becker, Kronenberg et al. 2005; Kramer, Luke et al. 2005; Hsu, McCulloch et al. 2006; Axelsson 2008; Teplan, Vyhnanek et al. 2010). Kidney damage associated with obesity was first recognised with the classification of obesity related focal segmental glomerular sclerosis in 1974 (Serra, Romero et al. 2008). Microalbuminuria, one of the first indicators of kidney damage, worsens with increasing adiposity, although the mechanisms relating obesity and albuminura are not

completely known, but are likely to be haemodynamic and/or metabolic (Gilardini, Zulian et al. 2010). Obesity related albuminuria is associated with increased renal blood flow and glomerular pressure, resulting in glomerular hyperfiltration which may increase albumin losses, but is reversed with weight loss (Chagnac, Weinstein et al. 2003). There is no widely accepted definition of hyperfiltration, other than an absolute increase in glomerular filtration rate, and the mechanisms of hyperfiltration in chronic disease states are not clear, although the renin-angiotensin-aldosterone system is thought to be involved, and increased glomerular capillary pressure and glomerular hypertrophy is evident in obesity (Helal, Fick-Brosnahan et al. 2012). With glomerular hyperfiltration, morphological changes occur, including increased glomerular size, basement membrane thickening and podocyte hypertrophy, which result in kidney damage, and ultimately reduced kidney function (Serra, Romero et al. 2008; Kato, Nazneen et al. 2009).

From a series of 6 818 kidney biopsies performed between 1986 to 2000, the prevalence of obesity related glomerulopathy (ORG) was first defined, as focal segmental glomerulosclerosis with glomerulomegaly or glomerulomegaly alone in patients with a BMI > 30 kg/m^2 (Kambham, Markowitz et al. 2001). A total of 103 cases of ORG were detected in the series (1.5%), and the prevalence increased from 0.2% between 1986 – 1990 to 2.0% from 1996 – 2000. 71 cases, with adequate clinical information (57 with focal segmental glomerulosclerosis with glomerulomegaly, and 14 cases with glomerulomegaly alone), were compared to 50 cases of idiopathic focal segmental glomerulosclerosis (I-FSGS), and those with ORG had more glomerulomegaly, less podocyte damage and fewer lesions of segmental sclerosis that those with I-FSGS (Kambham, Markowitz et al. 2001). Additionally, even though proteinuria was present in nearly 50% of the patients with ORG, these patients had lower incidence of oedema and nephrotic syndrome, indicating that ORG is a condition associated with proteinuria, but without the hypoalbuminuria and full

nephrotic syndrome seen more commonly in the I-FSGS group. Progression to end stage kidney disease or doubling of serum creatinine occurred less frequently in the ORG group than in the I-FSGS group, indicating that ORG may be a slowly progressive disease.

In a smaller case series studying the clinical outcomes of 15 patients with ORG and 15 patients with I-FSGS, patients with ORG developed worsening proteinuria and the 10-year renal survival was poor, with almost 50% of patients with ORG experiencing a doubling of serum creatinine, including 5 patients who reached end stage kidney disease requiring dialysis (Praga, Hernandez et al. 2001). A third series of kidney biopsies from 95 obese patients with normal kidney function and 40 normal weight controls was published in 2008 (Serra, Romero et al. 2008). 60 patients showed evidence of glomerulomegaly or FSGS in the obese group, compared to 1 patient in the control group. The obese group also displayed higher levels of globally sclerosed glomeruli, increased mesangial matrix and mesangial cell proliferation and greater podocyte hypertrophy than the control group (Serra, Romero et al. 2008). Additionally, BMI was the only factor predictive of glomerular lesions in the obese patients, compared to controls, after multivariate adjustment (Serra, Romero et al. 2008), indicating that obesity related changes in the kidney prior to any clinical manifestation of CKD, may increase the risk of developing CKD over time. These 3 clinical studies, demonstrating structural changes in the kidneys of obese patients, support the epidemiological findings linking obesity to the development and progression of CKD.

In addition to structural and functional adaptations contributing to obesity related kidney damage, inflammatory and metabolic effects have also been identified (Wu, Liu et al. 2006; Wahba and Mak 2007; Deji, Kume et al. 2009). Mice fed a high-fat, high-energy diet for 12 weeks gained weight and developed metabolic syndrome, with increased systolic blood

pressure, triglycerides and insulin resistance, when compared to mice fed either a standard diet, or an energy-reduced high fat diet. After 12 weeks, structural and functional kidney changes including lipid and macrophage infiltration in kidney tissue were evident in mice on the hypercaloric high energy, high fat diet, but not in mice on either the standard diet or the energy-reduced high fat diet (Deji, Kume et al. 2009), indicating that excess energy intake, rather than a high fat diet itself, induces changes in kidney tissue. These structural changes may be related to alterations in adipokines (signalling peptides secreted almost exclusively by adipose tissue), insulin resistance, and/or increased intra-abdominal pressure accompanying the weight gain leading to obesity (Kato, Nazneen et al. 2009). Therefore it is possible that obesity-related kidney damage occurs during weight gain, and may be related to altered production of adipokines and exhaustion of insulin homeostasis leading to insulin resistance.

In order to examine multiple factors related to the pathogenesis of ORG, gene expression profiles of biopsy-derived glomeruli from obese patients with ORG were studied (Wu, Liu et al. 2006). In 6 patients with obesity, proteinuria and biopsy proven ORG (Kambham, Markowitz et al. 2001), microarray analysis and real-time quantitative polymerase chain reaction (RT-qPCR) revealed a distinct up-regulation of gene expression for the inflammatory cytokines tumour necrosis factor-alpha (TNF-α) and its receptors and interleukin-6 (IL-6) signal transducer in the glomeruli of patients with ORG, compared to normal weight healthy controls. There was also abnormal regulation of the LDL-cholesterol receptor gene and increased expression of vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), glucose transporter 1 (GLUT-1) and the leptin receptor, which are involved in lipid metabolism and insulin resistance (Kambham, Markowitz et al. 2001). This study provided the first evidence that

inflammatory cytokines and their downstream pathways were likely to play a role in obesity related glomerular injuries.

Figure 3 outlines the possible relationships and pathways between increased weight gain, obesity and the mechanisms resulting in kidney damage and cardiovascular complications.

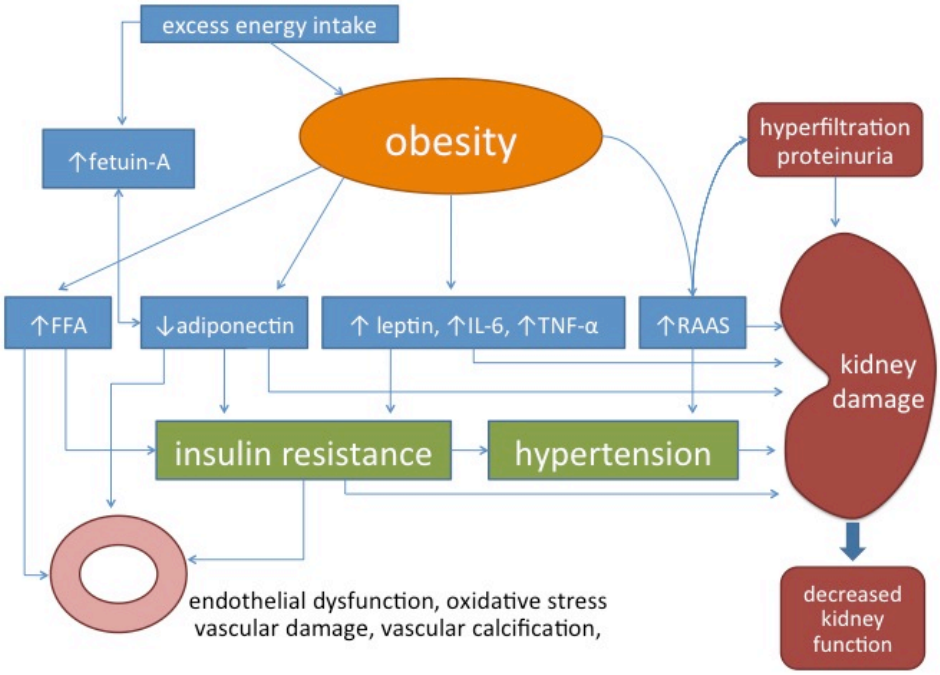


Figure 3: Mechanisms of obesity induced kidney injury

FFA – free fatty acids; IL-6 – interleukin 6; TNF-α – tumour necrosis factor-α; RAAS – renin angiotensin aldosterone system

Hepatic production of fetuin-A increases with obesity, and suppresses adipocyte adiponectin mRNA expression, induces insulin resistance in muscle and liver and increases IL-6 and TNF-α expression (Ix and Sharma 2010); low adiponectin levels and insulin resistance compromise protective mechanisms on podocytes and renal tubular cells leading to microalbuminuria (Fornoni 2010; Fang, Liu et al. 2013), inappropriate up-regulation of the RAAS system, increased reactive oxygen species and vascular endothelial dysfunction and kidney damage (Nistala and Whaley-Connell 2013); leptin increases due to a feedback inhibition mechanism which inhibits activation of leptin receptors (Myers, Leibel et al. 2010), increases sympathetic nervous system activity, inflammation, and increases TGF-β in the kidney (Wolf, Hamann et al. 1999).

ORG is not the only manifestation of obesity related kidney damage, and obesity accelerates the loss of renal function with other primary causes of CKD. There are several major, potentially reversible, mechanisms by which obesity may result in kidney damage leading to a reduction in kidney function over time; increased intra-abdominal pressure and

increased glomerular filtration, increased inflammation, and alterations in adipose tissue hormones (Ritz, Koleganova et al. 2011). Increased physical compression caused by excess adipose tissue surrounding the kidneys, and sympathetic activation of the renin-angiotensin aldosterone system (RAAS), resulting in increased renal blood flow leading to excess tubular sodium resorption, which, in turn, signals to increase vasodilation of the afferent arterioles (Kambham, Markowitz et al. 2001) and increased vasoconstriction of efferent arterioles, due to increased angiotensin II, leading to increased renal perfusion pressure, volume expansion, hypertension, hyperfiltration, glomerulomegaly, and eventually loss of nephrons and fibrosis (Wahba and Mak 2007; Sarafidis 2008).

The increase in gene expression of inflammatory factors and lipid dysmetabolism evident in ORG (Wu, Liu et al. 2006), together with the reduction in clearance of uraemic toxins in patients with CKD (Stenvinkel, Carrero et al. 2008), due to the reduced glomerular filtration rate, may lead to nephrotoxicity due to an amplified cytokine response from both increased production and decreased clearance of pro-inflammatory factors.

Adipose tissue is not simply a storage repository, but the largest endocrine organ in the body, secreting pleiotropic adipocytokines such as leptin, adiponectin and the inflammatory factors IL-6 and TNF-α (Axelsson, Qureshi et al. 2004). An increase in circulating leptin, which occurs with obesity due to leptin resistance, increases insulin resistance, promoting glomerular hypertrophy and glomeruloscerosis through up-regulation of TGF-β and insulin-like growth factors (Wolf, Hamann et al. 1999). Altered adipokines and the inflammatory state present in both obesity and CKD may be the link between metabolic syndrome, insulin resistance and vascular damage, culminating in atherosclerotic cardiovascular disease (CVD) in both chronic disease states (Pecoits-Filho, Barany et al. 2002; Addabbo, Mallamaci et al. 2007). Mechanisms of the cardiovascular complications in

CKD are related to endothelial dysfunction, inflammation, activation of the renin-angiotensin system, increased circulation of cytokines, and impaired bone mineral metabolism (Schiffrin, Lipman et al. 2007), although many of the specific pathways and mechanisms in obesity related kidney disease remain unknown.

Insulin has anti-inflammatory, anti-oxidant and anti-thrombotic effects alongside modulation of blood glucose levels. The insulin resistance evident in obesity is likely related to reduced insulin signal transduction caused by activation of inhibitory pathways by elevated pro-inflammatory cytokines IL-6, C-reactive protein (CRP) and TNF-α produced by adipose tissue and macrophages (Dadona, Chaudhuri et al. 2008). In CKD, peripheral insulin resistance is strongly and inversely correlated to kidney function - independent of diabetes (Crutchlow, Robinson et al. 2007) and body weight - and positively correlated with TNF-α and IL-6, and is known to reflect atherosclerosis in patients with CKD (Addabbo, Mallamaci et al. 2007). Additionally, insulin stimulates the production of TGF-β from renal mesangial and tubular cells, which is known to be involved in pathways leading to renal fibrosis (Sarafidis 2008).

Adipose tissue secretes adipokines, including leptin and adiponectin, which have pro- and anti-inflammatory properties and may be involved in insulin resistance, metabolic syndrome and atherosclerosis (Bobbert and Spranger 2008). Leptin functions as a chronic satiety signal, and modulates fatty acid oxidation and utilisation, enhancing insulin sensitivity (Stenvinkel, Lindholm et al. 2000). Paradoxically, circulating leptin concentrations increase with obesity, a mechanism often referred to as leptin resistance (Munzberg and Myers 2005). Leptin resistance is not fully understood, but occurs in part, due to a reduction in leptin receptor activation as a result the feedback inhibition signalling from the accumulation of signal transducer and activator of transcription – 3 (STAT-3)

induced suppressor of cytokine signalling – 3 (SOCS-3), and other mechanisms such as endoplasmic reticulum stress and inflammation, which lead to insulin resistance are thought to also contribute to leptin resistance (Myers, Leibel et al. 2010). Leptin has also been observed to exert pro-atherogenic effects (Dadona, Chaudhuri et al. 2008). Leptin levels also increase in CKD without increased body fat in patients with mild to moderate CKD, likely due to reduced leptin clearance (Guebre-Egziabher, Bernhard et al. 2005), and may be involved in several metabolic processes, including uremic anorexia, protein energy wasting (Fouque, Kalantar-Zadeh et al. 2007), and vascular calcification (Stenvinkel, Lindholm et al. 2000; Parhami, Tintut et al. 2001).

Adiponectin is a circulating adipokine produced by adipocytes (Goldstein and Scalia 2004). It has protective metabolic and vascular effects in non-CKD subjects and may work in anti-inflammatory pathways (Rabin, Kamari et al. 2005) by suppressing early events in the atherosclerotic process (Ouchi, Kihara et al. 1999). Adiponectin levels are reduced in obesity, negatively correlate with leptin and insulin resistance (Wiecek, Adamczak et al. 2007). Low adiponectin levels related to compromised endothelial function, which can result in accelerated atherosclerosis (Heber 2008). Reduced renal function obscures these relationships as adiponectin levels increase as kidney function declines. This largely reflects reduced adiponectin clearance, although uraemia and inflammation may also contribute (Barazzoni, Bernardi et al. 2007; Neiszporek, Witkowicz et al. 2007), possibly with adiponectin levels rising as a protective anti-inflammatory mechanism, concomitantly with an overwhelming inflammatory response. Therefore, in CKD, both high (Menon, Li et al. 2006) and low (Zoccali, Mallamaci et al. 2002; Iwashima, Horio et al. 2006) levels of adiponectin have been associated with increased CVD risk. Recent research indicates that adiponectin is a likely regulator of albuminuria, with a reduction in adiponectin related to increased albuminuria, reversible with adiponectin administration and normalisation of

podocyte foot process structure (Ix and Sharma 2010). These findings identified adiponectin as a possible link between adipose tissue and kidney cross-talk (Ix and Sharma 2010).

Fetuin-A, a peptide produced exclusively in the liver, is increased with obesity, and is associated with increased truncal obesity, and dyslipidaemia in haemodialysis patients (Axelsson, Wang et al. 2008; Chen, Chiu et al. 2009). Fetuin-A is known to play an important role in the inhibition of vascular calcification, and low fetuin-A levels are related to mortality in haemodialysis patients (Stenvinkel, Wang et al. 2005). Fetuin-A may also be involved in insulin resistance by suppressing adiponectin in adipose tissue (Ix and Sharma 2010). This reduction in adiponectin inactivates 5' adenosine monophosphate-activated protein kinase (AMPK), and the increased fetuin-A induces insulin resistance by blocking the insulin receptor tyrosine kinase, the net effect of which may be kidney damage through podocyte effacement and albuminuria (Ix and Sharma 2010). In a 1-year weight loss intervention study in obese children, fetuin-A levels were associated with insulin resistance and components of metabolic syndrome prior to weight loss, and both fetuin-A and insulin resistance decreased with weight loss (Reinehr, Roth et al. 2008). The relationships between fetuin-A, adiponectin and leptin in adipose tissue and the kidney offer some insight into the possible mechanisms of obesity related glomerulopathy, particularly podocyte damage, which warrant further study through weight loss interventions in obese patients with CKD.

Weight loss, inflammation and adipokines

As it became established that obesity was an inflammatory condition, the effects of weight loss interventions on the levels of inflammatory cytokines and adipokines began to be investigated. Early studies indicated that weight loss, achieved with energy reduced diets

and increased physical activity, is associated with reductions in IL-6, CRP, leptin, and increased adiponectin (Gallistl, Sudi et al. 2001; Esposito, Pontillo et al. 2003; de Luis, Aller et al. 2008; de Luis, Aller et al. 2009). The addition of orlistat, a lipase inhibitor that reduces fat absorption in the gastrointestinal tract by 30% (Guerciolini 1997), may enhance the effects of weight loss on reducing inflammation. In a randomised controlled trial of an energy-reduced diet, with or without Orlistat, the diet plus orlistat group demonstrated greater weight loss and body fat loss, as well as greater reductions in CRP and TNF-α than the diet alone group, after correcting for weight loss (Bougoulia, Triantos et al. 2006). This implies that either the greater reduction in fat mass, or another factor related to the use of orlistat itself, also contributes to reducing obesity-associated inflammation.

A review of the evidence relating to changes in adipokines and inflammatory markers with dietary based weight loss interventions was published in 2010 (Klimcakova, Kovacikova et al. 2010). Overall, the only adipokine consistently associated with weight loss is a decrease in leptin, which reflects a reduction in body fat mass. Total plasma adiponectin was not as sensitive to changes in body weight, and this may be related to the presence of different isoforms of adiponectin, with the high molecular weight isoform the most physiologically active in humans, which may be more sensitive indicator of active adiponectin in obesity. Studies of inflammatory markers such as IL-6 and TNF-α with weight loss were equivocal, with either no change or a decrease in these inflammatory markers, however, as these markers are not specific to adipose tissue, total serum levels do not necessarily reflect changes mediated by a reduction in adipose tissue with weight loss (Klimcakova, Kovacikova et al. 2010).

The effect of weight loss on inflammation and adipokines, via weight loss surgery, is addressed later in this chapter.

Obesity in Haemodialysis Patients

The prevalence of obesity in patients with end stage kidney disease requiring dialysis is now consistent with that in the general population (Kramer, Saranathan et al. 2006). Between 1994 and 2002 in the United States, the mean BMI at initiation of dialysis rose from 25.7 kg/m^2 to 27.5 kg/m^2 and now almost one third of incident dialysis patients are obese (Kramer, Saranathan et al. 2006). Similar data is not accessible in the United Kingdom as data on BMI at initiation of dialysis is incomplete in the Renal Registry (United Kingdom Renal Registry). However, it is likely that the pattern in the United States is indicative of the situation in the United Kingdom also, and the increase in the number of obese patients with end stage kidney disease requiring dialysis has implications for planning and providing dialysis services. (Zoccali, Kramer et al. 2009).

Increasing body size in the CKD population has resulted in an unexpected association between greater body mass index and improved survival in haemodialysis patients (Abbott, Glanton et al. 2004; Kalantar-Zadeh, Kopple et al. 2005; Chazot, Gassia et al. 2009), in contrast to that evident in the general "healthy" population (Rogers 2003), and in patients with non-dialysis CKD (Elsayed, Sarnak et al. 2008). However, not all studies show on-going improvement in survival with increasing BMI in obese patients. There may be a limit to the protective capacity of BMI, as no significantly greater survival advantage was evident for BMI between 31-37 kg/m^2 than for BMI of 29-31 kg/m^2 in patients followed up for 2 years (Johansen, Young et al. 2004), or with percentage body fat > 36% compared to 12 – 24% body fat, which was also associated with lower quality of life (Kalantar-Zadeh, Kuwae et al. 2006).

Yet the emerging relationship between obesity and its impact on CKD is complex. Further exploration of the observation that obesity is protective in haemodialysis patients failed to find this survival advantage in older haemodialysis patients followed for 7 years compared to obese controls followed for the same time period (de Mutsert, Snijder et al. 2007). Similarly, in a cohort of patients in the Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD) Study also followed up for 7 years, there was no relationship between BMI and mortality in patients older than 65 years, yet in obese dialysis patients less than 65 years, the age standardised adjusted mortality rate was 1.57 times higher than in dialysis patients with a normal BMI (Hoogeveen, Halbesma et al. 2012). Therefore, in contrast to older dialysis patients, younger obese dialysis patients have a higher risk of death than dialysis patients of normal BMI, and the relationship between BMI and mortality in older dialysis patients appears to be attenuated with longer follow up.

BMI is a surrogate marker of body composition, but is actually more reflective of total body size than total body fat or body fat distribution. The observation that higher BMI is more protective that normal BMI against mortality in haemodialysis patients may reflect the importance of lean body mass or nutritional status rather than body adipose tissues stores, in the context of BMI. Indeed, when other measures of adiposity are used to define obesity, the relationship becomes clearer. In a population of 537 Italian haemodialysis patients, both waist circumference and BMI were measured at baseline and patients were followed up for 2 years to determine the relationship between all-cause and cardiovascular mortality and obesity (Postorino, Marino et al. 2009). Whilst an inverse association between BMI and mortality was also found in this population, a direct relationship was evident between waist circumference and all cause mortality, indicating that excess abdominal adipose tissue increases mortality risk in haemodialysis patients.

Studies that have included surrogate measures of muscle mass in the survival analysis have found improved survival in those with greater estimated muscle mass. High pre-dialysis urinary creatinine plus high BMI was linked to reduced mortality risk when compared to normal BMI and higher creatinine, indicating that higher muscle mass, regardless of BMI was protective against mortality in haemodialysis patients (Beddhu, Pappas et al. 2003). Low mid-arm muscle circumference was associated with reduced 10-year survival in incident haemodialysis patients, even when BMI was > 25 kg/m^2 (Araujo, Kamimura et al. 2006). Protein energy wasting, often evident in obese and overweight patients, predicted mortality in overweight haemodialysis patients but BMI did not (Honda, Qureshi et al. 2007), again indicating that muscle is protective against mortality in this population. Whilst the literature lacks direct evidence that high muscle mass is the protective component of BMI against mortality in haemodialysis patients, these data suggest that good muscle mass is advantageous for survival (Mafra, Guebre-Egziabher et al. 2008) and that greater BMI above a certain threshold may not provide any further advantage due to the negative effects of excess abdominal adiposity.

Obesity and kidney transplantation

Obesity may limit treatment options in kidney failure as access to kidney transplantation is reduced once BMI > 35 kg/m^2 (Segev, Simpkins et al. 2008). In kidney transplant recipients with BMI > 35 kg/m^2 mortality increases and graft survival decreases when compared to patients with BMI 30 - 35 kg/m^2 (Cacciola, Pujar et al. 2008). Obese kidney transplant recipients have higher rates of surgical wound infections, delayed graft functioning and acute rejection, and longer than average length of hospital stay than non-obese kidney transplant recipients (Meier-Kriesche, Arndorfer et al. 2002; Gore, Pham et al. 2006). In a study that sought to distinguish between obese and morbidly obese patients to determine the effect on mortality and graft survival, obese patients with BMI > 35 kg

/m^2 had greater mortality and lower kidney graft survival after 1 and 5 years than obese patients with BMI 30-34.9 kg/m^2, but there was no difference in wound infection rates between the 2 groups (Cacciola, Pujar et al. 2008). The results indicated that patients with BMI > 35 kg/m^2 are a high-risk group for transplantation, with the highest risk period being the first year post-transplantation. The authors recommended that all obese patients be considered for transplantation based on individual cardiovascular risk factors rather than simply by BMI. Post-kidney transplant risk of cardiovascular morbidity also increases with increasing BMI. In a study of 1 105 post-kidney transplant patients categorised by BMI quartiles, increased incidence of congestive heart failure and atrial fibrillation occurred with increasing BMI, yet there was no difference in the myocardial infarction event rate by BMI quartile (Lentine, Rocca-Rey et al. 2008).

Weight loss interventions in obese patients with chronic kidney disease

Management of obesity is now an important consideration in patients with CKD, yet it may be even more complex than within the general population, given the additional limitations on dietary and fluid intake and reduced clearance of excess metabolites due to diminished or absent kidney function. Current practice guidelines for nutritional intervention in CKD provide very little guidance on the management of obesity in patients with CKD and the evidence is gleaned from epidemiological studies rather than clinical intervention trials (Fouque, Vennegoor et al. 2007; Wright and Jones 2010; Masoomi, Kim et al. 2011). There are very few studies investigating weight loss interventions for obesity in CKD. A recent systematic review and meta analysis reported on 12 studies in patients with CKD, proteinuria and glomerular hyperfiltration; 6 with exercise and/or dietary interventions and 6 investigating weight loss surgery (Navaneethan, Yehnert et al. 2009). Nine observational cohort studies, one retrospective analysis, 1 non-randomised trial and 2 randomised controlled trials were included in the analysis. The pooled results of these

studies demonstrated significant reductions in systolic blood pressure, proteinuria and glomerular hyperfiltration with weight loss. In patients with CKD, there was no change in kidney function with weight loss, although some studies reported a decline in kidney function in the control groups which may indicate that weight loss in obese patients with CKD may halt disease progression (Navaneethan, Yehnert et al. 2009).

A similar systematic review of the effect of intentional weight loss on proteinuria, reported on 5 randomised controlled trials and 8 uncontrolled trials (Afshinnia, Wilt et al. 2010). Weight loss was associated with significant reductions in microalbuminuria and proteinuria using meta-regression analysis, and weight loss with surgery was associated with a reduction in hyperfiltration. The authors commented on the limitations of the primary data sources which were of small sample size, many lacked control groups and most were conducted over relatively short time periods (Afshinnia, Wilt et al. 2010). Therefore, well-designed randomised controlled trials of intentional weight loss in obese patients across the spectrum of CKD are still required, to determine the effect on markers of kidney damage and measures of kidney function.

Lifestyle Interventions

Successful lifestyle-based interventions for weight loss in chronic kidney disease include energy restrictions ranging from 500 kilocalories (kcal) less than usual intake/day (Morales, Valero et al. 2003) , through 1 000-1 400 kcal/day meal plans (Solerte, Fioravanti et al. 1989; Praga, Hernandez et al. 1995), to low energy intakes of 700-900 kcal/day (Vasquez, Flock et al. 1984; Saiki, Nagayama et al. 2005) and a combination of 500 kcal less than usual intake/day, exercise and orlistat (Roche, Basel, Switzerland) therapy (Cook, MacLaughlin et al. 2008). The duration of these interventions ranges from 4 to 52 weeks,

however, detailed information on the dietary prescription and how it is monitored is often lacking in published reports.

Weight loss achieved is related to the level of energy restriction imposed. Over 4 weeks, balanced very low kcal meal replacements were utilised for 1-2 meals per day, to induce a 6 kg weight loss, which reduced proteinuria (Saiki, Nagayama et al. 2005). The study did not follow up patients after the 4-week intervention to determine whether weight was regained once the intervention ceased. Work by our group and others has found that moderate energy restriction of 500 kcal per day resulted in a similar level of weight loss over 12 months (Morales, Valero et al. 2003; Cook, MacLaughlin et al. 2008), and our follow up study demonstrated this level of weight loss was maintained for a further 12 months, in conjunction with exercise and orlistat (MacLaughlin, Cook et al. 2010).

In a cohort of obese non-diabetic women, improvements in glucose metabolism, but not blood pressure reduction or weight loss, were associated with a reduction in microalbuminuria following a 3 month lifestyle based weight loss intervention, suggesting that metabolic alterations such as insulin resistance - rather than altered glomerular dynamics - contribute to impaired kidney function in obesity (Gilardini, Zulian et al. 2010). One, small uncontrolled, study attempted to address the effects of a 20% energy reduction on adipokines, insulin resistance and inflammation in obese patients with diabetic nephropathy. After two months, minimal, non significant, weight loss occurred, and there was no change in leptin, adiponectin, insulin resistance or CRP (Kozlowska, Rydzewski et al. 2010). The dietary energy deficit did not appear sufficient to induce weight loss and there was no intervention in increase physical activity to increase energy expenditure. Further study of weight loss is warranted to determine the impact on novel cardiovascular risk factors such as leptin, adiponectin, IL-6, TNF-α, CRP, and endothelial function in

obese patients with CKD. However, levels of these signalling factors are influenced by reduced renal clearance and insulin resistance, metabolic syndrome with and without overt obesity in CKD, so defining mechanistic relationships between these factors and weight loss remains difficult.

A meta analysis of the effect of weight loss (surgical and non surgical) on kidney function demonstrated a pooled reduction in hyperfiltration of 23.7 ml/min (95% CI, 11.4 to 36.2), a 17% decrease from baseline (95% CI, 8% to 26%) (Afshinnia, Wilt et al. 2010), indicating that weight loss may reduce obesity-associated glomerular hyperfiltration, which can be a precursor to reduction in kidney function (Hostetter, Olson et al. 1981) and may delay or prevent progression towards overt, irreversible, kidney damage. However, in patients with BMI >35 kg/m^2, weight loss achieved with lifestyle interventions may remain inadequate for kidney transplantation access, and the factors associated with obesity related kidney function decline are likely to persist.

Weight loss surgery

Weight loss surgery leads to sustained weight loss, resolution of diabetes, and a reduction in traditional cardiovascular risk factors (Sjostrom 2000), and may provide a practical solution to increasing eligibility for kidney transplantation in obese patients with CKD. A recent Health Technology Assessment of weight loss surgery for obesity reported weight loss surgery as a more effective intervention for weight loss than non-surgical options; and is cost effective, particularly over the longer term (Picot, Jones et al. 2009).

Weight loss surgery is a more effective intervention for weight loss than medical treatments and is either purely restrictive to reduce the size of the stomach and limit food intake, or has an additional malabsorptive procedure (Picot, Jones et al. 2009) (Figure 4). Restrictive

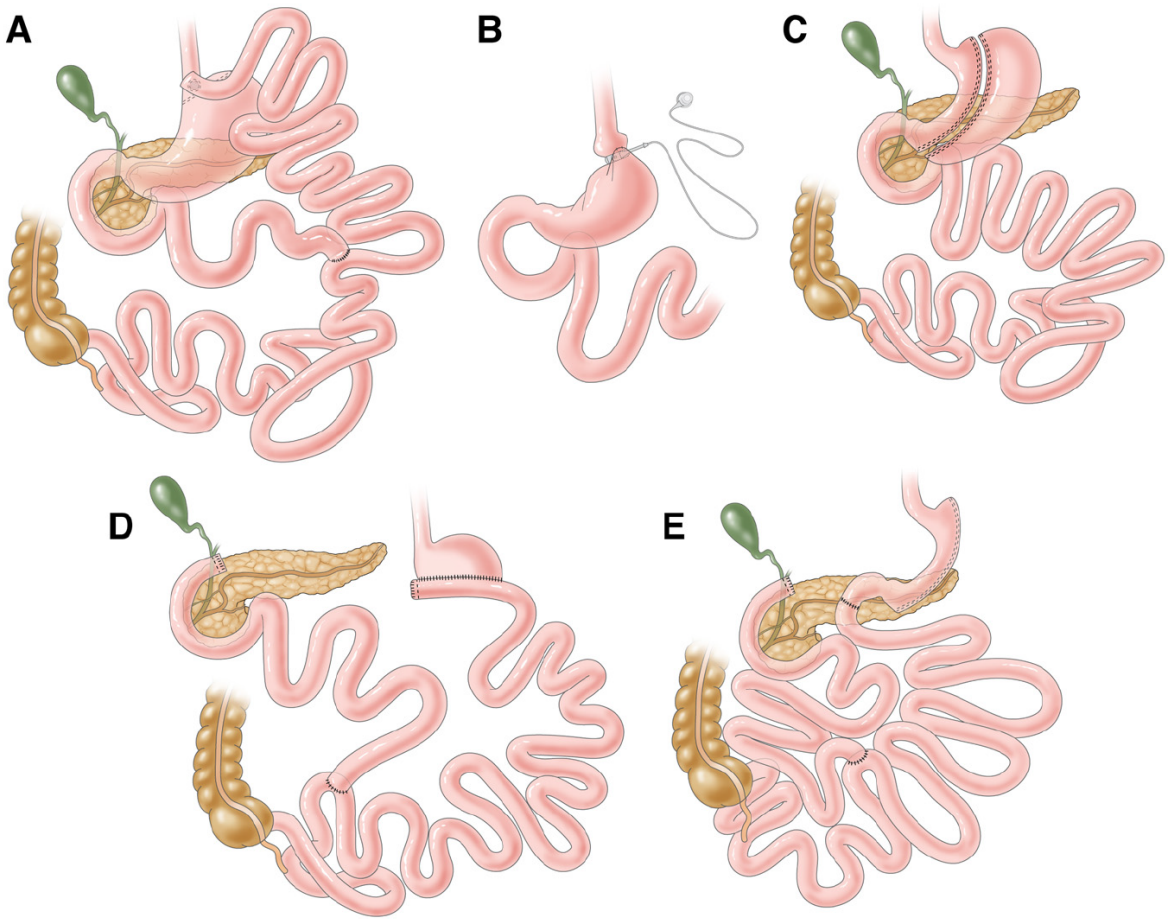


Figure 4: Weight loss surgery techniques A – Roux–en Y Gastric bypass, B – Adjustable Gastric Band, C – Sleeve Gastrectomy, D – Biliopancreatic Diversion, E – Biliopancreatic Diversion with Duodenal Switch (Adapted from (Bradley, Magkos et al. 2012))

procedures include adjustable gastric banding, vertical banded gastroplasty (no longer performed routinely) and sleeve gastrectomy. Laparoscopic sleeve gastrectomy is a novel form of restrictive weight loss surgery to create a long tube-like stomach after subtotal gastric resection of the fundus and body, and has recently been accepted as an approved bariatric surgery procedure by the American Society for Metabolic and Bariatric Surgery (ASMBS Clinical Issues Committee 2009). Restrictive and malabsorptive procedures, bypassing part of the small intestine to reduce nutrient absorption, are the Roux-en-Y gastric bypass, biliopancreatic diversion and biliopancreatic diversion with duodenal switch (Picot, Jones et al. 2009). In the Roux-en Y bypass, a small stomach is created and

anastamosed to the proximal jejunum, with the biliopancreatic limb reinserted into the distal jejunum, leaving a considerable length of common limb for digestion. The biliopancreatic diversion consists of a horizontal gastrectomy anastamosed to the ilium, with a short common limb after rejoining the proximal end of the dissected ilium 50cm before the terminal ilium. A modification of this procedure, with duodenal switch, has a vertical sleeve gastrectomy with a duodenal-ileal anastomosis and ileal to ileal resection 100cm from the terminal ilium (Bradley, Magkos et al. 2012).

A 2004 systematic review and meta analysis of all forms of weight loss surgery, except sleeve gastrectomy, included 22 094 patients in 136 studies, and reported a mean excess weight loss of 61.2% (95% CI 58.1%-64.4%) for all patients, with drastic improvements in sleep apnoea, hypertension, hyperlipidaemia and diabetes (Buchwald, Avidor et al. 2004). Weight loss surgery has been associated with a reduction in mortality in patients who had undergone weight loss surgery when compared to age, gender and weight matched controls in three large observational cohort studies (Christou, Sampalis et al. 2004; Adams, Gress et al. 2007; Sjostrom, Narbro et al. 2007). Yet one study also reported an increase in deaths from accidents and suicide in the surgery group, compared to the control group (Adams, Gress et al. 2007).

The Swedish Obese Subjects study is the largest, prospective, controlled study of mortality following weight loss surgery. After a mean follow up period of 10.9 years, the multi-variable adjusted risk of death was lower in the surgery group compared to the control group (adjusted hazard ratio 0.71; 95% confidence interval (CI) 0.54, 0.92; $p = 0.01$) (Sjostrom, Narbro et al. 2007). Additionally, the incidence of stroke and myocardial infarction were also reduced after weight loss surgery (adjusted hazard ratio 0.67; 95% CI 0.54, 0.83; $p < 0.001$) (Sjostrom, Peltonen et al. 2012). The effect of weight loss surgery on

blood glucose control in obese patients with type-2 diabetes has recently been investigated in 2 randomised controlled trials of weight loss surgery compared to best medical care (Mingrone, Panunzi et al. 2012; Schauer, Kashyap et al. 2012). Resolution of diabetes occurred in 37 - 42% of patients 12 months after weight loss surgery in one study (Schauer, Kashyap et al. 2012) and after 2 years, there was a 75 - 95% reduction in diabetes post bariatric surgery in the second study (Mingrone, Panunzi et al. 2012). Therefore, weight loss surgery appears an effective treatment for obesity, which may reduce mortality, cardiovascular events and diabetes in obese patients, when compared to no surgical treatment.

Several studies have examined the effect of weight loss surgery on markers of inflammation, adipokines and insulin resistance. Weight loss surgery using either the Roux-en-Y bypass or sleeve gastrectomy is associated with improvements in insulin resistance and adiponectin, and reductions in leptin, CRP, IL-6 and metabolic syndrome after twelve months (Vilarrasa, Vendrell et al. 2007; Hofso, Nordstrand et al. 2010; Woelnerhanssen, Peterli et al. 2011; Illan Gomez 2012; Illan-Gomez, Gonzalvez-Ortega et al. 2012). A reduction in the inflammatory cytokine IL-18 was associated with a decrease in insulin resistance and triglycerides 12 months after gastric bypass surgery, and adiponectin levels increased (Vilarrasa, Vendrell et al. 2007). No association was reported between adiponectin and inflammatory markers 12 months post surgery (Vilarrasa, Vendrell et al. 2007; Illan Gomez 2012; Illan-Gomez, Gonzalvez-Ortega et al. 2012), although relationships between the changes in variables with weight loss were not examined. Furthermore, one of these studies also included a comprehensive lifestyle programme study arm, and reported that improvements in glycaemic control and decreased diastolic blood pressure were related to weight loss of > 10% regardless of treatment group (Hofso, Nordstrand et al. 2010).

Weight loss surgery in obese patients with CKD is sparsely reported in the literature. There are 11 intervention studies (excluding individual case reports) reporting on the effect of weight loss surgery on renal outcomes. Five studies report on obese patients with normal or elevated kidney function and 6 studies include patients with defined CKD.

Observational studies of gastric bypass and gastric banding in obese patients with CKD suggest that weight loss surgery can induce significant weight loss and reduction in glomerular hyperfiltration and proteinuria (Chagnac, Weinstein et al. 2003; Navarro-Diaz, Serra et al. 2006; Agrawal, Khan et al. 2008), may improve or stabilise estimated kidney function (Alexander and Goodman 2007; Alexander, Goodman et al. 2009; Navaneethan and Yehnert 2009), urinary inflammatory markers (Bueter, Dubb et al. 2010) or serum creatinine (Schuster, Teodorescu et al. 2011), and improve candidacy for kidney transplantation (Newcombe, Blanch et al. 2005; Koshy, Coombes et al. 2008; Takata, Campos et al. 2008). However, these studies have either been conducted in obese patients without overt CKD or have reported retrospectively on small numbers of selected patients with varying stages of CKD and without comparison to matched controls not undergoing weight loss surgery.

Observational studies of gastric bypass surgery in obese and super-obese patients with early signs of kidney disease demonstrated significant weight loss and reduction in proteinuria, especially in patients with diabetes and metabolic syndrome (Chagnac, Weinstein et al. 2003; Navarro-Diaz, Serra et al. 2006; Agrawal, Khan et al. 2008). In a case series analysis of 45 obese patients with varying severity of CKD undergoing gastric bypass surgery, 14 patients then underwent kidney transplantation and 31 did not. Of these remaining 31 patients, 9 patients (29%) demonstrated an improvement or stabilisation in either

proteinuria or serum creatinine, including the cessation of dialysis in 2 patients for some time after gastric bypass surgery (Alexander, Goodman et al. 2009). This study reported positive outcomes of transplantation, or improvement or stabilisation of kidney function for half the study population, but did not comment on the outcomes in the rest of the studied population. Gastric bypass surgery in an uncontrolled retrospective analysis of 25 obese patients with stage 3 CKD improved estimated kidney function from 47.9 ml/min/1.73m^2 at baseline to 61.6 ml/min/1.73m^2 after 12 months, with a reduction in BMI from 49.8 kg/m^2 to 34.5 kg/m^2 over the same time period (Navaneethan and Yehnert 2009). Whilst this data is encouraging, this study used an estimate, rather than a direct measurement, of kidney function indexed to standardised body surface area, which underestimates kidney function in obese patients and introduces bias when longitudinal data is compared without accounting for the changes in body weight and body surface area over time (Delanaye, Radermecker et al. 2005), so the results must be interpreted cautiously.

There is emerging evidence that both the gastric bypass and adjustable gastric banding procedures may lead to kidney related complications in a minority of patients. A sub-population of obese patients develops hyperoxaluric nephrolithiasis after gastric bypass, which increases the risk of formation of calcium oxalate crystals within the kidney tissue and can cause chronic oxalate nephropathy and deterioration in kidney function (Nelson, Houghton et al. 2005; Sinha, Collazo-Clavell et al. 2007; Nasr, D'Agati et al. 2008; Matlaga, Shore et al. 2009). Gastric bypass was associated with an increased likelihood of diagnosis and treatment of kidney and upper urinary tract stone formation (nephrolithiasis) in 4 693 obese subjects when compared 4 693 BMI, age, gender, diabetes status and antihypertensive treatment matched controls who did not undergoing gastric bypass surgery (OR for diagnosis of urinary calculus 1.71; 95% CI 1.44, 2.04; and OR for any

urological procedure 3.65; 95% CI 2.60, 5.14) (Matlaga, Shore et al. 2009). A case series of 60 patients with nephrolithiasis after gastric bypass was identified at the Mayo Clinic-Rochester between 1985 and 2004, with approximately 30% of patients identified as having pre-existing nephrolithiasis prior to gastric bypass surgery (Sinha, Collazo-Clavell et al. 2007).

A more serious complication in a small minority of patients has been reported. Thirteen cases of chronic oxalate nephropathy, developed as a result of gastric bypass surgery, have been reported in the literature - including two cases from the Mayo Clinic-Rochester series - with 10 of these 13 cases progressing to stage 5 kidney disease requiring dialysis (Nelson, Houghton et al. 2005; Nasr, D'Agati et al. 2008). In many of these cases patients also had long standing diabetes and hypertension, which whilst unlikely to be the catalyst for the sudden deterioration in kidney function in this sub-group, may have contributed to the rapidity of the decline.

Several factors known to be associated with nephrolithiasis and oxalate nephropathy have been identified in patients after gastric bypass, including increased urinary oxalate and calcium-oxalate supersaturation, reduced urine volume and decreased urinary citrate (Sinha, Collazo-Clavell et al. 2007; Park, Storm et al. 2009). However, restrictive weight loss surgery procedures (gastric banding and sleeve gastrectomy) are not associated with increased urinary stone risk factors, including urinary oxalate, when compared to gastric bypass in obese patients (Semins, Asplin et al. 2010). This indicates that the surgery induced malabsorption and increase in bile salts production, secondary to the reduction in the length of small intestine, rather than weight loss itself leads to hyperoxaluria and calcium oxalate supersaturation.

Gastric banding may be complicated by the combination of CKD and post kidney transplantation immunosuppression, and may require further investigation, as two cases of complications with gastric banding post kidney transplantation have been reported (Buch, El-Sabrout et al. 2006). In one case, a gastric band inserted prior to kidney transplantation subsequently became eroded after kidney transplantation and was removed. The second case report relates to gastric banding performed secondary to weight gain post kidney transplantation; two months after insertion, the band migrated downwards, causing gastric obstruction, and also required subsequent removal (Buch, El-Sabrout et al. 2006). Both band erosion and migration may have been related to immunosuppression treatment associated with organ transplantation (Buch, El-Sabrout et al. 2006).

Therefore, whilst gastric bypass and gastric banding procedures are effective in inducing weight loss and may improve kidney function and increase the likelihood of patients undergoing kidney transplant, they may worsen kidney function in a small minority of patients.

There remains a distinct lack of well-designed studies on the treatment of obesity in patients with CKD and as yet, no studies have reported on the use of sleeve gastrectomy in this patient population. Sleeve gastrectomy is a relatively novel form of restrictive weight loss surgery in which a tube-like stomach is created after two-thirds subtotal gastric resection of the fundus and body, and is usually performed laparoscopically (ASMBS Clinical Issues Committee 2009). Functional stomach integrity is maintained with a reduced stomach volume and as it is a purely restrictive procedure there is no malabsorption; nor is a foreign object introduced into the body. As these characteristics prohibit the occurrence of the aforementioned side effects of other weight loss surgery

procedure, sleeve gastrectomy has the potential to be a promising solution for morbidly obese patients with CKD.

A 2009 systematic review of 36 studies of 2 570 patients undergoing sleeve gastrectomy reported weight loss of 36-85% of excess body weight loss with follow up from 3 to 60 months (Brethauer, Hammel et al. 2009). Reported complication rates ranged between 0-24% for all studies and between 0-15% for studies including more than 100 patients; 30-day mortality was 0.19% and incidence of gastric leak was 2.2%, bleeding 1.2% and post operative strictures 0.6% (Brethauer, Hammel et al. 2009). Weight loss after sleeve gastrectomy is attributed to both the reduction in stomach volume and to a post surgical reduction in plasma ghrelin levels - a hormone produced in the stomach that is associated with hunger signalling (Langer, Hoda et al. 2005; Karamanakos, Vagenas et al. 2008).

The safety and effectiveness of laparoscopic sleeve gastrectomy was compared to laparoscopic Roux-en-Y gastric bypass and laparoscopic gastric banding using data from the American College of Surgeons Bariatric Surgery Centre Network Accreditation Program (Hutter, Schirmer et al. 2011). Data from 28 616 patients in 109 hospitals were collected from 2007 to 2011, and 12-month outcomes were reported in 2011. Of the 944 patients who underwent sleeve gastrectomy surgery, there were 8 patients (0.74%) with renal insufficiency and 8 patients (0.74%) on dialysis. Sleeve gastrectomy had a 30-day complication rate of 5.6%, which was similar gastric bypass (5.9%), and both procedures had a higher complication rate than gastric banding (1.4%). There was no difference in 30-day or 12-month mortality between the three procedures, with a combined 30-day mortality rate of 0.12%. The effectiveness of sleeve gastrectomy lay between gastric bypass and gastric banding. The mean decrease in BMI at 12 months was 11.9 kg/m^2 for sleeve gastrectomy, compared to 7.1 kg/m^2 for gastric banding and 15.3 kg/m^2 for gastric

bypass (Hutter, Schirmer et al. 2011). Similar data has recently been reported in the first report from the UK National Bariatric Surgery Registry (Welbourn, Fiennes et al. 2011).

As the sleeve gastrectomy procedure is a relatively quick, effective weight loss procedure that does not involve insertion of a foreign body or require adjustments, immediately restricts food intake and is not associated with increased risk of nephrolithiasis, it may be seen as advantageous over adjustable gastric banding and gastric bypass procedures (Himpens, Dapri et al. 2006; Karamanakos, Vagenas et al. 2008; Semins, Asplin et al. 2010; Brethauer, Hammel et al. 2009). Disadvantages may include irreversibility of gastric resection, possible longer term gastric dilation which may lead to weight re-gain, and an increased short term risk of leak and bleeding compared to gastric banding (Himpens, Dapri et al. 2006). However, long-term data on the safety and efficacy of weight loss with sleeve gastrectomy over more than 2 years remains limited and the safety and efficacy of the sleeve gastrectomy has yet to be established in obese patients with CKD.

Well-designed prospective studies with matched surgical intervention and non-surgical intervention treatment groups are still lacking, particularly in obese patients with stages 2-5 CKD, and there are no published studies examining the use of the relatively novel sleeve gastrectomy procedure in obese patients with CKD. Calls for interventional studies on obese patients with CKD have been expressed repeatedly in the literature, in order to determine both the effects of weight loss on kidney function, and the benefits of weight loss to this patient group (Locatelli, Pozzoni et al. 2006; Cignarelli and Lamacchia 2007; Wang, Chen et al. 2008; Navaneethan, Yehnert et al. 2009; Othman, Kawar et al. 2009; Afshinnia, Wilt et al. 2010; Chang and Kramer 2012).

Furthermore, since the intervention studies in this thesis were commenced, 2 recently published papers have quantified the risk associated with weight loss surgery in patients with kidney disease or renal failure. In a retrospective review of the American College of Surgeons National Surgical Quality Improvement Program Participant Use File, 6 930 patients with CKD stages 2-5 were identified among 27 736 patients undergoing weight loss surgery between 2006 and 2008 (Turgeon, Perez et al. 2012). Risk of complications increased as stage of CKD increased with an increase in the odds ratio of 1.3 for each stage of CKD. Overall, the risk remained <10% in patients with stage 5 CKD, which given the high morbidity and mortality in patients with stage 5 CKD, is still an acceptable risk, but one which patients should be informed of (Turgeon, Perez et al. 2012). Similarly, in a study of in-patient mortality post weight loss surgery using information from the United States Nationwide Inpatient Sample, chronic renal failure was associated with increased risk of death post weight loss surgery (adjusted odds ratio 2.7) (Caterson, Finer et al. 2012). The studies reporting increased risk of complications in patients with CKD (Caterson, Finer et al. 2012; Turgeon, Perez et al. 2012), did not include the sleeve gastrectomy procedure, so the mortality risk and complication rate in obese patients with CKD undergoing sleeve gastrectomy remains unknown. These retrospective analyses, and those studies reporting on oxalate nephropathy, nephrolithiasis and gastric band migration and erosion, are based on gastric bypass and gastric banding procedures, and provide new evidence that weight loss surgery in patients with CKD carries an increased risk of complications and mortality, than in patients without kidney disease.

Summary

Whilst evidence is accumulating for the contribution of obesity to the development and progression of CKD, there remains a lack of evidence on the mechanisms contributing to kidney damage and there are few interventional studies of the effects of significant weight

loss on CKD parameters. It is known that weight loss can improve albuminuria, proteinuria and hyperfiltration. One retrospective study demonstrated an improvement in estimated kidney function with weight loss surgery (Navaneethan and Yehnert 2009). No prospective, controlled studies have been identified with measured kidney function, or kidney transplantation listing as a primary outcome following a weight loss intervention in obese patients with CKD. Relationships between adipokines, obesity, inflammation, insulin resistance, CKD and mortality have been identified, although there are no studies examining the effect of weight loss on mortality, and just one small uncontrolled study addressing inflammation, insulin resistance and adipokines in obese patients with established CKD (Kozlowska, Rydzewski et al. 2010).

Intervention studies examining changes in levels of adipokines and inflammatory cytokines known to be modified in both obesity and CKD may add to the body of knowledge of the mechanisms involved in obesity related kidney changes and might prove useful in identifying targets for therapeutic agents in the future. Weight loss with weight loss surgery may be a useful model for determining the effects of obesity on the kidney over a relatively short period of time. Sleeve gastrectomy has not yet been studied in obese patients with CKD, yet it appears to be a suitable procedure to utilise, as it should not expose patients to the known risks of bypass surgery or gastric band placement in patients with CKD. Carefully designed and diligently controlled investigations are required into the effect of planned weight loss in obese patients with CKD, in order to determine to effect of weight loss on kidney function, inflammatory signalling markers and cardiovascular risk markers, such as endothelial repair mechanisms and vascular elasticity and responsiveness.

Clinical outcomes

Intervention studies aiming to demonstrate a relationship between weight loss and a reduction in morbidity associated with CKD, such as a reduction in cardiovascular events, have yet to be published. There are several factors related to CKD such as dyslipiaemia, accumulation of waste products and a chronic inflammatory state that may be detrimental to vascular function and perhaps these may counteract the beneficial effects of weight loss. It is crucial that the effect of weight loss on cardiovascular disease risk factors in patients with CKD is understood, in order to determine whether or not pursuing weight loss treatments is beneficial for patients. Major benefits would be improvement in kidney function or acceptance for kidney transplantation, and secondary benefits would likely include reduction in inflammation and improvement in vascular functional measures. Long term outcomes, such as cardiovascular events and mortality should also be studied, but are beyond the scope of this PhD project.

Whilst we understand that weight loss in patients with, or approaching, kidney failure, is likely to assist patients to become eligible for kidney transplantation, the effect on kidney function, and morbidity and mortality is unknown. The timeframe of this clinical intervention based research limits its focus on major clinical outcomes, but it may have implications for the prevention of obesity related progression of CKD, creating greater access to kidney transplantation, improving quality of life and contributing to the knowledge of the mechanistic effects of obesity on the kidney through its reversal with weight loss.

Exploration of the literature in the area revealed information on indicators of early kidney disease and novel cardiovascular risk markers derived from epidemiological and observational studies. Yet, very few interventions studies on weight loss in obese patients with CKD exist. As the candidate's clinical group has expertise in delivering an effective

intervention treatment for obesity in patients with CKD, it was a natural progression to study the mechanisms involved by examining changes in markers of cardiovascular risk and kidney function with weight loss over time. Weight loss surgery provides a useful model for rapid weight loss in order to investigate the resultant changes in metabolic and functional measures relating to kidney function, inflammation, adipose tissue signalling peptides and vascular function, as well as quality of life.

Overall Aim

The overall aim of this research is to determine the effect of weight loss interventions on cardiovascular and all cause mortality, kidney function, quality of life and access to kidney transplantation in obese patients with chronic kidney disease. Additionally, weight loss surgery is being used to explore the effects of significant weight loss on novel cardiovascular risk factors, such as inflammation, adipose tissue hormones, insulin resistance and vascular function, and the complications and adverse events associated with sleeve gastrectomy in obese patients with chronic kidney disease will be monitored.

Chapter 2: Participation in a structured weight loss programme and all-cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease

Chapter Summary

Obesity is associated with higher all-cause mortality. Whilst weight loss of 5 to 10 % of body weight in overweight and obese populations is associated with favourable changes in blood pressure, blood lipids and glycaemic control, the relationship between weight loss and mortality in overweight and obese populations is less clear. Intentional weight loss in obese patients with established cardiovascular risk factors may concur a survival advantage. Obesity, cardiovascular disease and diabetes are all risk factors for the development and progression of chronic kidney disease (CKD), and weight loss interventions are recommended for obese patients with CKD, yet studies on the long term outcomes of weight loss interventions in obese patients with CKD are lacking.

A retrospective cohort study was conducted to determine if participation in a weight loss programme impacts upon all-cause mortality and cardiovascular morbidity in obese patients with CKD. All patients with a body mass index (BMI) of > 30 kg/m^2 or >28 kg/m^2 with at least one co-morbidity (hypertension, diabetes or dyslipidemia) referred to an established weight management programme (WMP) from 2005-2009 were eligible for inclusion in the study cohort.

The WMP is a structured weight loss programme of a low-fat, energy reduced renal diet, exercise and pharmacotherapy delivered by a renal dietitian and renal physiotherapist. The primary outcome was time to a combined event of all cause mortality, myocardial infarction, stroke, or hospitalisation for congestive heart failure, in patients who chose to participate in the WMP, compared to those who did not participate. Univariate analysis

was performed with Kaplan Meier curves with log rank test and a multivariable adjusted Cox regression analysis was undertaken to adjust for potential confounding factors for the combined outcome. Additionally, factors contributing to kidney transplant waitlisting in obese patients with chronic kidney disease were explored using multiple logistic regression analysis. 169 obese patients with CKD commenced the WMP and 169 did not - becoming the observational control group (CON). There were no significant differences between groups for age, body mass index (BMI), gender, ethnicity, hypertension status, or kidney function at baseline, although CON included more patients with diabetes than WMP (49% vs 38%, p=0.03). Kaplan Meier survival analysis with log rank test for time to the primary combined outcome of cardiovascular morbidity and all cause mortality differed between groups (p=0.03). Cox regression analysis with adjustment for baseline BMI, diabetes, age, kidney function, gender, hypertension and ethnicity indicated that patients in WMP had a significantly longer event free period than those in CON (adjusted Hazard Ratio 0.452, 95% CI 0.26 - 0.80; p = 0.007). Participation in the WMP did not increase the likelihood of kidney transplantation waitlisting (OR 1.06, 95% CI 0.39 - 2.87; p = 0.9). Lower baseline BMI and greater weight loss over 12 months were the only factors related to kidney transplantation waitlisting (adjusted R^2=0.426). Due to the observational study design these relationships are limited to associations only, and causality cannot be determined. Furthermore, as this was a single centre study the findings may not be applicable to other populations of obese patients with CKD. This study suggests that participation in a structured weight loss programme may be associated with improved survival in obese patients with CKD but did not impact upon the likelihood of kidney transplantation waitlisting.

Introduction

Obesity is a risk factor for both the development of chronic kidney disease (CKD) and the decline in kidney function leading to end stage kidney failure. The efficacy of our renal Weight Management Programme (WMP) has been demonstrated previously, with patients achieving and sustaining 8% weight loss up to 2 years (MacLaughlin, Cook et al. 2010). However, weight loss in obese patients with CKD has not been directly related to improvements in blood pressure or favourable changes in blood lipid profile (MacLaughlin, Sarafidis et al. 2012), possibly due to the diminished haemodynamic control and dyslipidaemia associated with CKD (Levin 2003).

Generally, weight loss of 5-10% in the overweight and obese general population is associated with reduction in blood pressure, improvement in blood lipid profile and reduced insulin resistance leading to improved glycaemic control (Pasanisi, Contaldo et al. 2001). It is now established, from a systematic review and meta analysis extracting data from 97 studies, that obesity, using standardised reference categories for BMI, is associated with a higher risk of all-cause mortality (Flegal, Kit et al. 2013). Yet recent reviews of the effect of weight loss on mortality in overweight and obese populations in observational studies indicate that overall, the impact of weight loss on mortality is unclear, and weight loss has been associated with increased all-cause and cardiovascular mortality, decreased mortality and no association with mortality in observational and experimental studies (Poobalan, Aucott et al. 2007; Simonsen, Hundrup et al. 2008; Harrington, Gibson et al. 2009). The relationship between weight loss and mortality may be different between men and women, although confounding by other variables cannot be excluded in these predominantly observational studies (Poobalan, Aucott et al. 2007; Simonsen, Hundrup et al. 2008), particularly the intention to lose weight (Simonsen, Hundrup et al. 2008; Harrington, Gibson et al. 2009).

In the Copenhagen City Heart Study - an observational study of 19 329 randomly selected Danish citizens - weight change over 5 years was monitored, and mortality was recorded from the Danish Civil Registry for up to thirty years (Ostergaard, Gronbaek et al. 2010). In the 3 078 obese and overweight subjects at baseline, who either lost weight or maintained weight during this period, weight loss was significantly associated with all-cause mortality. In those who commenced physical activity during the observation period, weight loss was not associated with increased mortality when compared to those subjects who remained inactive throughout the study. The initiation of exercise may indicate intent to lose weight in this group, and appeared protective. As this study was not designed to discriminate between intentional and unintentional weight loss, the results should be interpreted cautiously.

In a review of studies designed to observe the effects of intentional weight loss on mortality, 9 out of 31 potentially relevant studies met the inclusion criteria of intentional or voluntary weight loss, with mortality as an outcome (Simonsen, Hundrup et al. 2008). These 9 studies were predominantly observational studies of population cohorts, with weight loss, and intentionality, as self reported findings. Four studies found no relationship between weight loss and mortality, 2 studies reported decreased mortality and 3 studies reported increased mortality. Potential confounders of the relationship between intentional weight loss and mortality were discussed, including baseline BMI, alcohol and smoking history, physical activity levels, socio-economic status, and rapid versus gradual weight loss. Additionally, intentionality was recorded only once in each study, therefore, both intentional and unintentional weight loss may have occurred in any subject despite classification of weight loss, as intentionality may change throughout the study observation period (Simonsen, Hundrup et al. 2008).

Concomitant changes in lifestyle habits occurring with weight loss or in the post weight loss period, such as changes in physical activity, and/or dietary intake, smoking status, and alcohol consumption, may also influence future mortality, either directly or indirectly as a consequence of diseases leading to unintentional weight loss. Co-morbidities may account for some of the variability in study findings, however, due to the conflicting results of the studies reviewed and the potential unaccounted for confounders, the authors report that the relationship between intentional weight loss and mortality in apparently healthy populations cannot be adequately addressed in observational studies and randomised trials may more appropriate for addressing this question. The relationship between weight loss and mortality in the apparently healthy population remains equivocal, and there are no prospective, randomised controlled trials conducted to specifically examine the effect of intentional weight loss, in obese patients, on mortality as the primary study outcome.

In a secondary analysis of older adult patients, enrolled in a randomised controlled trial with a weight loss treatment group, to determine the effect of intentional weight loss on all cause mortality in older overweight or obese adults, there was no difference in mortality between the weight loss and non weight loss groups, after 12 years of follow up (Shea, Nicklas et al. 2011); indicating that there may be no benefit of weight loss on mortality in overweight and obese adults over 60 years of age. The greatest weight loss in the group not randomised to a weight loss intervention was associated with a 2.5 times higher risk of mortality than in those who lost less weight, yet this effect was not evident in the group randomised to a weight loss intervention. Thus, even though this analysis was of a randomised trial of weight loss rather than an observational study, weight loss intentionality was not ascertained, and it is possible that both intentional and unintentional weight loss has been captured in the analysis.

Additional analyses of the Sibutramine Cardiovascular OUTcomes (SCOUT) randomised controlled trial of sibutramine versus placebo for weight loss indicated that maintained weight loss across all treatment groups was significantly related to a reduction in cardiovascular mortality (Caterson, Finer et al. 2012). Intentional weight loss achieved via specific weight loss programmes in populations of patients with existing co-morbidities, such as diabetes and cardiovascular disease, are associated with a lower likelihood of mortality (Williamson, Thompson et al. 2000; Caterson, Finer et al. 2012), or cardiovascular morbidity (Eilat-Adar, Eldar et al. 2005), indicating that intentional weight loss may reduce cardiovascular morbidity and all cause mortality in populations with established cardiovascular disease risk factors. The presence of co-morbid risk factors is likely to influence any relationship with mortality, and undetected co-morbidities may confound studies in apparently healthy populations.

The relationship between intentional weight loss and mortality and cardiovascular morbidity has not previously been explored in obese patients with CKD. Obesity, cardiovascular disease and diabetes are all risk factors for the development and progression of CKD (Gelber, Kurth et al. 2005; Coresh, Selvin et al. 2007; Hsu, Iribarren et al. 2009), yet studies on the long term outcomes of weight loss interventions in obese patients with CKD are lacking. Recent evidence also suggests that 50% of patients with CKD have actively attempted weight loss (Navaneethan, Kirwan et al. 2012), indicating that obesity and overweight may be of concern to the patient population, and weight loss treatments are being sought.

Study Aim

This study aims to determine if participation in a weight loss programme impacts upon all-cause mortality and cardiovascular morbidity in obese patients with CKD.

Primary Hypothesis

The primary hypothesis is that participation in a structured weight management programme in obese patients with CKD will decrease the likelihood of pre-specified cardiovascular morbidity and all cause mortality, compared to obese patients with CKD who do not participate in the programme.

Secondary Hypothesis

The secondary hypothesis is that participation in a structured weight management programme in obese patients with CKD will increase the likelihood of kidney transplantation waitlisting in patients who are considered ineligible due to a high body mass index, compared to obese patients with CKD who do not participate in the programme.

Methods

Study population

All male and female patients, aged 18-80 years, under the care of a Nephrologist and with a BMI of > 30 kg/m^2, or > 28 kg/m^2 with at least one co-morbidity (hypertension, diabetes or dyslipidaemia), referred to the renal Weight Management Programme (WMP) at King's College Hospital, London, between January 2005 and December 2009 were eligible for inclusion in the study cohort.

All referred patients were invited to attend a 60-minute information session designed to provide further information about the programme and outline the responsibilities of the treating team and expectations and commitment required from participants. Potential participants who attended this session were given a 7-day food and activity record to complete and return in a pre-addressed, postage paid envelope. Return of the food and

activity record indicated consent to participate in the WMP group, and upon return of the record, patients were given their first appointment for the WMP clinic.

Patients who either did not attend the information session or did not return the 7-day food and activity record were entered into the contemporaneous observational control (CON) group. These patients continued to attend their usual care visits to the Consultant Nephrologist. Study data were recorded at either WMP clinic visits or usual care visits. All data were coded so that patients were unable to be identified and reporting of these data complied with the King's College Hospital research ethics policy.

Weight loss intervention

There were four components to the WMP: a low-fat energy-reduced renal diet, regular exercise, and use of the anti-obesity medication orlistat (Xenical; Roche Products, Basel, Switzerland), implemented using behavioural therapy techniques. The programme was led by an experienced Renal Dietitian (the candidate) and a Renal Physiotherapist, with support from the Consultant Nephrologist and a Renal Pharmacist as needed. Patients attended the WMP clinic for the initial baseline assessment, then monthly during the 6-month intervention period, and for monitoring and support at 9 and 12 months. Individualised diet and exercise regimens were developed with all patients using structured dietary education with motivational interviewing (Miller and Rollnick 2002) and cognitive behavioural therapy techniques to address barriers to lifestyle change; including food and activity diaries, stimulus control, through process evaluation, cost benefit analysis and problem solving (Cooper, Fairburn et al. 2003). Treatment was structured and standardised, with checklists for each session developed to act as both cue for and record of the session.

Dietary Intervention

A low-fat energy-reduced renal diet, depending on body size, physical activity level and dietary intake at baseline, was negotiated with each patient based on food preferences and appropriate for each patient's CKD stage. Dietary modification was based on estimated energy requirement using the Schofield equation for resting metabolic rate based on age, gender, and actual body weight, plus an appropriate activity factor between 20% - 40%, less 600 kcal/day for weight loss. Protein intake was optimised for the stage of CKD for each patient, at 1.0 g protein/kg ideal body weight (IBW)/day for stage 3 CKD, 0.8 - 1.0 g of protein/kg IBW/day for stage 4 CKD, and 1.2 g of protein/kg IBW for stage 5 CKD patients requiring dialysis (EDTNA/ERCA Dietitians' Special Interest Group 2002). Fat intake was limited to < 70 g/day to minimise the side effects of orlistat. The remaining calories were consumed from carbohydrate sources, with higher fibre choices encouraged when possible. All patients were encouraged to modify sodium intake to a "no added salt" diet level, of 80-100 mmol sodium per day (EDTNA/ERCA Dietitians' Special Interest Group 2002). Potassium and phosphate intake were modified according to serum biochemistry and kidney function (Abbott, Glanton et al. 2004; Renal Association 2007).

Adherence to dietary recommendations was monitored from the patients' food diaries - written food intake records every month for up to 6 months. At each visit, dietary education was provided as required, using a range of standardised modules (Table 2) with

Table 2: Standardised dietary education modules used in the Renal Weight Management Programme

Size Matters – portion control	Identifying high risk situations
Eating a low fat diet	Meal Plan
Low fat cooking + quick recipes booklet	Problem solving techniques
Eating Out	Keeping going

written information and practical exercises plus visual content. Patients generated at least 2 dietary goals each month from baseline to month 6, facilitated by motivational interviewing techniques used by the dietitian (Miller and Rollnick 2002)

Exercise Intervention

Personal exercise plans were developed based on the patient's individual current level of exertion and co-morbid conditions, and incorporated aerobic and muscular endurance activities to improve functional capacity and increase energy expenditure. Frequency was at least 3 days/week, exercise duration was increased as tolerated up to 60 minutes, and intensity was set at Borg's Scale of Perceived Exertion level of "somewhat hard" to "hard" (Borg 1998). The exercise plan was adapted at each monthly visit in line with improvements in exercise capacity to facilitate a progressive training effect.

Pharmacotherapy

Patients were prescribed orlistat at the standard dose of 120 mg 3 times/day throughout the study. Orlistat is a locally acting gastrointestinal lipase inhibitor that reduces the absorption of dietary fat by approximately 30%. On-going education about the mechanism of action and the importance of limiting dietary fat intake to reduce the gastrointestinal side effects associated with the drug's inhibition of dietary fat absorption was provided.

Study endpoints

The primary endpoint of the study was the combined event rate of all cause mortality, and the first occurrence during the study period of a cardiovascular event. A cardiovascular event was defined as myocardial infarction, stroke or congestive heart failure requiring hospitalisation and treatment with ionotropes, vasodilators or diuretics.

Events were recorded from electronic patient medical records during the retrospective data collection period between December 2010 and March 2011. Electronic patient records include details of patient medical history, current and previous medications, hospital admissions, details of events occurring between regular nephrology clinical out-patient visits, and date of death.

The secondary endpoints were placement on the waiting list for kidney transplantation and all cause mortality. Records of kidney transplantation status, including waitlisting were recorded in the study database from the renal speciality electronic patient database records.

Measurements and Definitions

A retrospective analysis of prospectively collected data was performed. Baseline and follow up data were collected and recorded prospectively by the candidate for all patients from their initial WMP clinic appointment between January 2005 and December 2009, with final data for cardiovascular events and mortality recorded between December 2010 to March 2011.

Demographic data including age, gender, ethnicity, weight history, estimated kidney function, and treatment clinic modality were collected at baseline. Height was measured to the nearest 0.01 m using a fixed stadiometer. Body weight was measured to the nearest 0.1 kg in light clothing on a digital scale, and BMI was calculated as weight (kg)/height $(m)^2$. For dialysis patients, estimated oedema free body weight was recorded at each clinic visit. Resting sitting BP was recorded using an automated sphygmomanometer and an appropriate-sized cuff. Kidney function was assessed by eGFR, for all patients except those undergoing dialysis, and was calculated with the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation using serum creatinine, age and sex, and corrected

for ethnicity (Levey, Bosch et al. 1999; Levey, Greene et al. 2000). Patients were classified to a stage of CKD according to the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative definition (2002). Attendance at each of the 9 WMP sessions was documented for each patient. The number of WMP visits attended, body weight, weight change, orlistat use, orlistat side effects, and co-morbidities, were recorded prospectively at WMP visits, for up to 12 months.

Baseline for patients in the CON group was defined as the date of the initial information session the patient was invited to attend. Body weight, height, BMI, eGFR (for non-dialysis patients), treatment clinic modality, and body weight 12 months after baseline, were extracted retrospectively from electronic medical records.

Hypertension status and diabetes status were determined for all patients at baseline. Hypertension status was defined as systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg; or > 130/80 mm Hg in patients with proteinuria or diabetes; or the patient was prescribed at least one of the following classes of antihypertensive agents: angiotensin converting enzyme inhibitors, angiotensin receptor II blockers, beta-receptor blockers, calcium-channel blockers and thiazide-type diuretics. Hypertension was actively treated with multiple agents in WMP and CON groups and during follow up attending physicians could openly modify antihypertensive agents.

Diabetes status was defined as the presence of type 1 or type 2 diabetes recorded in the electronic medical record or self-reported by the patient, or prescription of medication for controlling blood glucose level from any one or more of the following classes of drugs for the treatment of diabetes: sulphonylureas, biguanides, glitazones, DPP4 inhibitors/incretin

mimetics, Alpha-glucosidase inhibitors, prandial glucose regulators and insulin/insulin analogues.

Statistical analyses

Data were analysed with SPSS version 17.0 (SPSS; Chicago, IL). Normally distributed variables were expressed as mean ± standard deviation (SD), and skewed distributions reported as median (interquartile range, IQR).

In order to detect a 33% reduction in the expected combined event rate in the WMP group with 70% power and accepting a 5% probability of type 1 error, with a ratio of one to one for intervention to control participants, 230 patients were required in each group. This calculation was based on a combined event rate of 30% in the sample population of obese patients with CKD and an assumption that the event rate would be reduced to 20% in the WMP group.

Comparisons between groups were performed using Student t-tests for normally distributed, or Mann-Whitney U tests for non-parametric, continuous variables and Chi squared tests for categorical variables, with Fisher's Exact Test for categorical variables with small cell counts (< 5 per group).

Univariate analyses of both the time to the combined event and the time to all cause mortality alone were conducted. Kaplan Meier curves were constructed and log rank tests were performed to determine if the time to the combined event or mortality alone differed between groups. Further modelling was then performed to determine the effect of co-variants on the unadjusted model, using multivariable Cox regression analyses. The crude model was adjusted for diabetes, hypertension, eGFR ≥ 15 ml/min/1.73m^2, age, gender,

ethnicity, baseline BMI and 12-month weight change. Hazard ratios (HR) were reported with 95% CI.

Logistic regression modelling was performed to determine whether listing for kidney transplantation during the study follow-up period differed between the WMP and CON groups. Patients with a functioning kidney transplant and those with stages 1 and 2 CKD were excluded, as they were unlikely to require kidney transplantation over the period of the study. Other factors included in the model were baseline BMI, age, gender, ethnicity and weight loss during the first 12 months post baseline.

Results

369 patients were referred to participate in the WMP over the study period. Nine patients with baseline BMI < 28 kg/m^2 were excluded. 185 (51.4%) patients elected to join the WMP and 175 (48.6%) patients did not enrol in the WMP, and became the observational control (CON) group (Figure 5). Three patients were excluded due to missing data, and 4 patients were excluded, 1 for each of the following reasons: sleeve gastrectomy weight loss surgery during study period; concurrently prescribed exenatide, an incretin mimetic agent known to induce weight loss (Waugh, Cummins et al. 2010); pregnancy at 12 month follow up; and significant worsening oedema through the study. All 15 patients on peritoneal dialysis were also excluded from this analysis due to non-equivalent distribution between

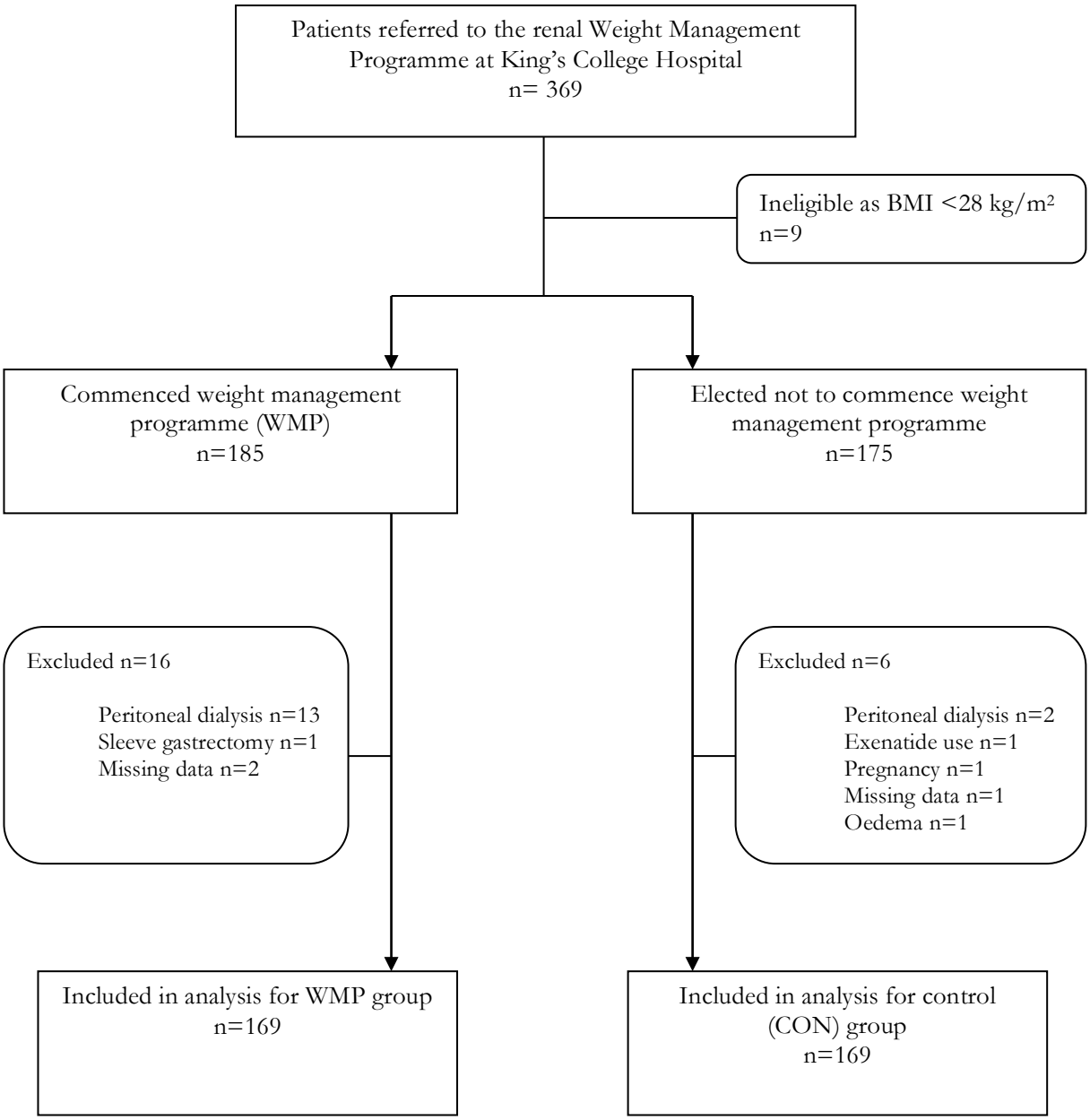


Figure 5: Flowchart outlining the process of deriving the study sample population of obese patients with chronic kidney disease

groups (13/15 in WMP and 2/15 in CON), leaving 169 patients in the WMP group and 169 patients in the CON group at baseline.

The mean age of participants was 52.0 (±12.8) years, with a median BMI of 35.3 (28.7 to 41.9) kg/m^2. 55% were male, 47% were White and 40% were Black, with the remaining 13% defined as Asian or other ethnicity. 94% of patients were hypertensive and 44% had diabetes. There were no significant differences between groups for age, BMI, gender,

ethnicity, hypertension status, or renal treatment modality at baseline (Table 3). The CON group included more patients with diabetes than the WMP group (49% vs 38%, p = 0.03).

Table 3: Baseline characteristics (mean ± SD, % or n) of obese patients with chronic kidney disease referred to a structured weight loss programme 2005-2009

Characteristic		Weight Management Programme (n = 169)	Control (n = 169)	p
Age (yrs)		52.3 ± 12.9	53.3 ± 12.7	0.478
Gender	Male (%)	51	58	0.184
	Female (%)	49	42	
Ethnicity (n)	White	81	79	0.837
	Black	65	70	
	Asian	19	15	
	Other	4	5	
Treatment modality (n)	Nephrology or Renal-Diabetes Clinic	72	82	0.113
	Pre-dialysis Clinic	48	31	
	Post Transplantation	28	26	
	Haemodialysis	21	30	
Diabetes (%)		38	49	0.03
Hypertension (%)		92	96	0.167
Body Mass Index (kg/m^2)		36.6 (± 5.3)	34.5 (± 5.1)	0.17

n, number of patients; SD, standard deviation

After 12 months, the mean (±SD) weight loss in all patients who commenced the WMP was 4.3 kg (± 5.5 kg) and 1.9 kg (± 6.6 kg) in all patients in the CON group (p = 0.001).

Over the 6 years of cohort observation, the median follow up period was 32.1 (6.5 to 57.5) months, and 55 events occurred. The combined event rate was 12% in the WMP group and 20% in the CON group (p=0.055) (Table 4), therefore the absolute event rate was 40% higher in the CON group than the WMP group. Univariate analysis of time to the combined outcome of all cause mortality and cardiovascular morbidity, using Kaplan Meier analysis with log rank test, demonstrated a significantly longer time to event in the WMP group, compared to the CON group (p = 0.032), indicating that participation in the WMP is associated with improved survival. The Kaplan Meier curves began to separate within 12

months and remained so for up to 60 months (Figure 6) although the curves did begin to converge again after 5 years.

Table 4: Combined all cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease referred to a structured weight loss programme 2005-2009

Event	Weight Management Programme (WMP) (n = 169)	Control (CON) (n = 169)	p
Combined Event	21	34	0.055
Death	11	21	0.06
MI	4	7	0.54
Stroke	5	2	0.45
CHF hospitalisation	1	4	0.37

MI - myocardial infarction; CHF congestive heart failure

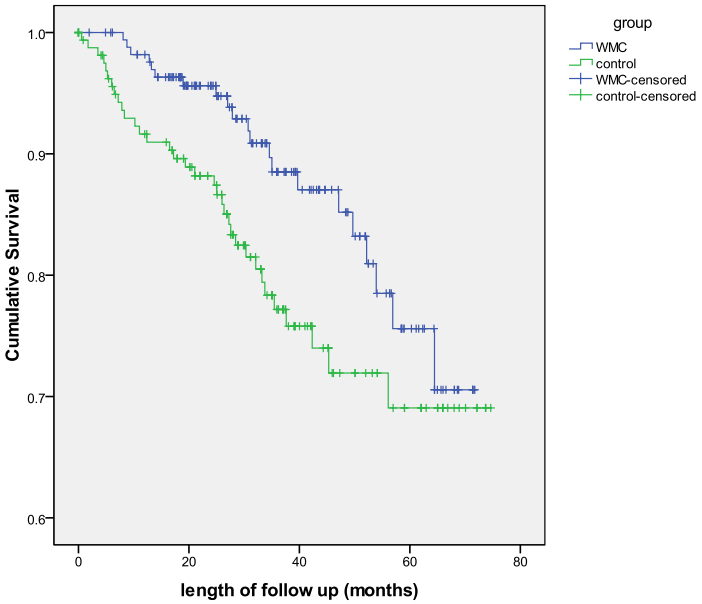


Figure 6: Kaplan Meier curves of combined all-cause mortality and cardiovascular morbidity in obese patients with chronic kidney disease referred to a weight loss programme 2005-2009 (p = 0.032 for log rank test)

Cox Regression modelling was used to determine the effect of participating in the WMP on the time to the combined event using unadjusted and multivariable models. Possible confounding variables were added to the model one at a time in the following order: diabetes, hypertension, eGFR (≥ 15 ml/min/1.73m^2 when compared to < 15

ml/min/1.73m^2, including haemodialysis), age + gender + ethnicity, and baseline log-transformed BMI (Table 5).

Table 5: Hazard ratios for combined mortality and cardiovascular morbidity outcome in obese patients with chronic kidney disease attending the Weight Management Programme from 2005-2009

Model		β (Hazard ratio)	95% CI for β	P
1	unadjusted model of WMP compared to CON	0.556	0.32 to 0.96	0.032
2	Model 1 + Diabetes	0.612	0.35 to 1.06	0.078
3	Model 2 + Hypertension	0.588	0.34 to 1.02	0.059
4	Model 3 + eGFR ≥15ml/min/1.73m^2	0.539	0.31 to 0.93	0.028
5	Model 4 + age + gender + ethnicity	0.482	0.28 to 0.84	0.010
6	Model 5 + baseline BMI	0.452	0.26 to 0.80	0.007

CI, confidence interval; CON, control group; eGFR, estimated glomerular filtration rate; BMI, body mass index; WMP, weight management programme group

In the unadjusted analysis, participation in WMP predicted a longer time to the combined event of all-cause mortality and cardiovascular morbidity, compared to the CON group (model 1). This association was weakened after adjustment for diabetes and hypertension (models 2 and 3). In models 4 and 5, additional adjustment for kidney function, age, gender and ethnicity strengthened the model and patients in the WMP group continued to be less likely to experience a shorter time to the combined outcome of death or cardiovascular event than those in the CON group (Model 5 adjusted HR 0.482, 95% CI 0.28 - 0.84; p = 0.01). After further adjustment for log-transformed baseline BMI (model 6) the association between a longer event-free period for the combined event in the WMP group (adjusted HR 0.452, 95% CI 0.26 - 0.80; p = 0.007), was maintained.

An additional model was created to include adjustment for 12-month weight change (model 6 plus 12 month weight change). The association between improved survival and

the WMP group was attenuated with adjustment for weight change, but remained significant (adjusted HR 0.519, 95% CI 0.28 - 0.97; p = 0.04).

In order to establish the robustness of the relationship between survival and attendance at the WMP, the Kaplan Meier Analysis with log-rank test was repeated for all cause mortality alone, to remove any bias occurring through the adjudication of the classification of the pre-determined cardiovascular events measured, and remained significant (p = 0.024). The fully adjusted multivariable Cox Regression model suggests that WMP participants were less likely to have a shorter time to death than those in the CON group (adjusted HR 0.378, 95% CI 0.172 - 0.829; p = 0.015), after adjustment for diabetes, hypertension, kidney function, age, gender, ethnicity and log-transformed baseline BMI.

During the study observation period, 131 patients otherwise met the criteria for kidney transplantation waitlisting, except for BMI, and 68 were in the WMP group and 63 in the CON group. 19 patients in each group were added to the kidney transplantation waiting list, which was 28% of the eligible WMP group and 30% of the eligible CON group (p = 0.78). 7/68 patients (10%) in the WMP group and 10/63 patients (16%) in the CON group underwent kidney transplantation during the study period.

The logistic regression analysis examining factors related to kidney transplantation waitlisting, compared to not waitlisting for kidney transplantation, is summarised in Table 6. Participation in the WMP did not increase the likelihood of kidney transplantation waitlisting (OR 1.06, 95% CI 0.39 - 2.87; p = 0.91). Lower baseline BMI and greater weight loss over 12 months were the only factors related to kidney transplantation waitlisting (adjusted R^2 = 0.426). For every 1.0 kg/m^2 increase in baseline BMI, the likelihood of kidney transplant waitlisting decreased by 33%, and for every 1.0 kg of weight

loss achieved over 12 months, the likelihood of transplant waitlisting increased by 15%. Age, gender, and ethnicity did not affect the likelihood of kidney transplantation waitlisting in this study. The likelihood of multicolinearity in the model was low assessed by examining the poor correlation between variables and the size of the standard error of the mean for all variables. The correlations between variables were poor and the standard error of the mean was less than 5 for all variables, indicating mulicolinearity was not present in the model.

Table 6: Multivariable logistic regression for factors related to qualifying for listing for kidney transplantation in obese patients with chronic kidney disease referred to a weight loss programme 2005-2009

Parameter	Odds Ratio (β)	95% CI for β	P
Group (WMP compared to CON)	1.06	0.39 to 2.87	0.91
Baseline BMI	0.67	0.56 to 0.80	<0.001
Weight loss during first 12 months	1.15	1.05 to 1.26	0.003
Age	0.97	0.97 to 1.02	0.25
Gender	1.82	0.67 to 4.96	0.24
Ethnicity	0.65	0.23 to 1.85	0.42

WMP - weight management programme; CON - control group; BMI - body mass index; CI - confidence interval; Group reference category is CON, Gender reference category is Men, Ethnicity reference category is White

Discussion

This study has examined and compared the time to the combined outcome of all-cause mortality and cardiovascular morbidity in a population of obese patients with CKD who were referred for weight loss treatment. There were significantly more primary events in the CON group than in the WMP group. Patients who elected to join the WMP were significantly more likely to have a longer event-free period than those in the CON group, who chose not to participate in the structured weight loss programme, even after adjustment for possible confounding variables including baseline co-morbidities, age, gender, ethnicity, baseline BMI, kidney function, and weight change. To the candidate's

knowledge, this is the first study to report on participation in a weight loss programme and the combined outcome of mortality and cardiovascular morbidity in obese patients with CKD. Furthermore, this study did not show any impact of participation in a weight loss programme on the likelihood of being wait-listed for kidney transplantation.

The relationship between the combined outcome of all cause mortality and cardiovascular morbidity (defined as the occurrence of myocardial infarction, stroke, or hospitalisation for congestive heart failure) and participation in a structured weight loss programme for patients with CKD appeared to be partially attributable to the known risk factors for cardiovascular disease; diabetes and hypertension. Correction for these 2 factors attenuated the relationship between WMP participation and the combined outcome, however further adjustment for age, gender and ethnicity counterbalanced the influence of diabetes and hypertension, and the relationship regained significance. Furthermore, when the model was corrected for kidney function, the adjusted HR for the relationship between treatment group and combined mortality and cardiovascular morbidity continued to demonstrate an advantage for patients participating in the WMP. Given that there is a known greater mortality and increased risk of cardiovascular disease as kidney function declines (Schiffrin, Lipman et al. 2007; Weiner, Tighiouart et al. 2007), this indicates that participation in the WMP may be protective for patients with all levels of kidney function.

Importantly, there was no apparent disadvantage to participating in a weight loss programme for obese patients with CKD, regardless of kidney function. Epidemiological studies demonstrate a survival advantage attributable to higher BMI in patients with kidney failure requiring haemodialysis (Abbott, Glanton et al. 2004; Johansen, Young et al. 2004; Kalantar-Zadeh, Kopple et al. 2005; Kalantar-Zadeh, Streja et al. 2010), although not all studies support this relationship. Higher muscle mass may be protective, and further

adjustments for age and increasing the length of study follow up ameliorate the relationship between higher BMI and survival (Beddhu, Pappas et al. 2003; de Mutsert, Snijder et al. 2007; Hoogeveen, Halbesma et al. 2012). The finding in this study that participation in the WMP may be protective for all patients with CKD, including patients with stage 5 CKD on haemodialysis, supports the conclusions of the latter studies (Beddhu, Pappas et al. 2003; de Mutsert, Snijder et al. 2007; Hoogeveen, Halbesma et al. 2012), and may indicate that high levels of body fat are not necessarily protective in haemodialysis. Therefore, participation in weight loss programmes by obese patients requiring haemodialysis should not be discouraged.

Whilst the findings in studies of weight loss and survival in the overweight and obese apparently healthy population are equivocal, previous studies examining the relationship between all cause mortality, cardiovascular mortality or cardiovascular morbidity and intentional weight loss in overweight and obese patients with existing co-morbidities indicate that weight loss may be beneficial for long term outcomes (Williamson, Thompson et al. 2000; Eilat-Adar, Eldar et al. 2005; Caterson, Finer et al. 2012). The findings of the present study concur with these studies and support the hypothesis that intentional weight loss is likely to be beneficial when existing co-morbidities known to increase cardiovascular disease risk are already present.

The relationship between CKD and cardiovascular disease is bi-directional (Stenvinkel, Carrero et al. 2008), and cardiovascular risk increases progressively with declining kidney function (Vanholder, Massy et al. 2005). Mechanisms of cardiovascular complications in CKD are related to inflammation, increased circulation of cytokines, endothelial dysfunction, activation of the renin-angiotensin system and impaired bone mineral metabolism (Schiffrin, Lipman et al. 2007). Weight loss in obese patients without CKD

has been associated with reduction in the inflammatory markers IL-6 and CRP (Gallistl, Sudi et al. 2001), improved insulin sensitivity, and increased adiponectin (Esposito, Pontillo et al. 2003), reduced endothelial dysfunction (Pierce, Beske et al. 2008), and a reduction in carotid vessel wall volume, an emerging measure of carotid atherosclerosis (Shai, Spence et al. 2010). Dietary restriction plus orlistat led to greater reductions in triglycerides and inflammatory markers, than dietary restriction alone, in obese women during a 6-month weight loss programme (Bougoulia, Triantos et al. 2006), and our previous work has suggested that a reduction in systolic BP was related to increased adherence to the WMP in obese patients with CKD (MacLaughlin, Sarafidis et al. 2012). As these cardiovascular risk factors were not measured in the present study, it is not possible to suggest which, if any, of these changes occurred in patients participating in the WMP, and what the effect on macro- and micro-vascular disease may be over the study observation period, as improvements in many of these factors is likely to be associated with a slowing of the rate of progression of cardiovascular disease over decades, rather than over a shorter term. However, a reduction in carotid vessel wall volume was evident over 2 years with modest weight loss of 5 kg and associated most strongly with a reduction in BP (Shai, Spence et al. 2010), indicating that changes brought about by weight loss can influence atherosclerotic processes over the relatively short term.

Weight loss in kidney transplantation waitlisted haemodialysis patients has been associated with increased mortality (Molnar, Streja et al. 2011). However, this finding was generated in a study not restricted to overweight and obese patients, and the weight loss observed was deemed to be unintentional (Molnar, Streja et al. 2011), which is known to be associated with mortality in patients requiring haemodialysis (Campbell and MacLaughlin 2010). The slight attenuation of the relationship between the combined mortality and cardiovascular morbidity outcome following adjustment for weight loss in the present

study may indicate that some degree of unintentional weight loss occurred in the control group; but it is more likely that the attenuation of the effect indicates that weight loss is one, but not the only, contributing factor to the risk reduction.

The study did not achieve its target sample size of 230 patients in each group. However, as the actual difference in the combined event rate between the WMP and CON groups was 40%, rather than the predicted 33%, a smaller sample size was adequate to demonstrate a significant treatment effect for participation in the WMP on all cause mortality and cardiovascular morbidity in both unadjusted and adjusted regression models.

There was no difference in the number of patients qualifying for kidney transplantation waitlisting between the WMP and CON groups, over the course of the study. Baseline BMI and weight loss over 12 months were the only variables related to kidney transplantation waitlisting in this study. Further analyses of the baseline BMI and weight loss in the CON group patients achieving transplant waitlisting during the study support this finding. Mean weight loss in those patients who were listed for kidney transplantation during the study was 5.0% in the WMP group and 4.3% in the CON group. Therefore, the level of weight loss in CON group patients who were waitlisted for kidney transplantation, was similar to the 4.5% weight loss achieved in the WMP group overall, and was substantially greater than the overall mean weight loss in the CON group. Patients who were listed for kidney transplantation in the CON group, had a mean baseline BMI of 31.6 kg/m^2, compared with the overall mean baseline BMI of 34.5 kg/m^2 for the CON group. Kidney transplant waitlisting may be a sufficient motivating factor to assist obese patients to lose weight, as weight loss, rather than participation in the WMP, was related to kidney transplantation waitlisting in this study. It should also be noted that kidney transplantation waitlisting is not dependent upon BMI or weight loss alone, as cardiovascular status, age,

cause of kidney disease, functional status and co-morbidities are also considered (Segev, Simpkins et al. 2008) when assessing eligibility for kidney transplant waitlisting.

There are several limitations to this study which should be acknowledged. The major limitation of this study is that allocation to treatment or control was not randomised, therefore, the relationship between treatment and the combined outcome cannot be directly attributed to participation in the WMP. By design, this study cannot account for unmeasured factors or residual confounding, and factors such as the ability to travel to the hospital based clinic in order to participate in the WMP, socio-economic status, literacy and education level, social supports and motivation to change lifestyle related health behaviours, may account for the relationship observed. Additionally, the dataset is relatively small for a time to event analysis, so the number of factors able to be included in a multivariable adjusted model of risk must be limited, to avoid overcorrection of the model and obtaining a statistically significant relationship by chance. However, the size of the sample is reasonably large for a weight loss intervention carried out in a single centre, and there is a reasonably even distribution of patients with all stages of CKD within each group. Furthermore, the groups are well matched at baseline for characteristics likely to impact upon the primary outcome of all cause mortality and cardiovascular morbidity, apart from the prevalence of diabetes, which was higher in the CON group. Together, these attributes reduce the likelihood that the relationship between commencing a weight loss programme and achieving a longer combined-event free period, is due to confounding or chance. The question of whether the relationship is due to an unmeasured variable, such as motivation to lose weight and adopt healthier behaviours such as increasing physical activity, can only be addressed by a randomised controlled trial, where these factors are likely to be equal across all groups studied. A randomised controlled trial of weight loss interventions in obese patients with CKD powered to examine the effect of

weight loss or participation in a weight loss programme on survival, would have the added benefits of being sufficiently robust to examine a number of secondary outcomes that may impact upon the primary event, and hence may contribute to determining the mechanisms involved in the decreasing risk of cardiovascular morbidity or all cause mortality.

Other limitations of the present study include the absence of correction for existing cardiovascular disease, statin use and albuminuria. A new meta-analysis found that statin use is associated with decreased mortality in patients with stages 1-4 CKD (Palmer, Craig et al. 2012), and albuminuria has also recently been found to contributed to mortality risk in patients with CKD (Hallan, Matsushita et al. 2012), however neither of these associations were known at the outset of the study. Statin use is highly prevalent in this study population and the majority of patients would have been prescribed statin therapy, and as information on albuminuria status is inconsistent across all stages of CKD in clinical practice, it was not included in the dataset. Similarly, as the major risk factors for cardiovascular disease - hypertension, diabetes, and CKD - were included in the adjusted analyses, additional correction for existing cardiovascular disease may have over corrected the model, due to the likely high co-linearity with the predisposing risk factors listed above. Furthermore, any deaths or events occurring early in the observation period are unlikely to have been altered by the lifestyle changes or weight loss, and conversely, this study was also unable to elucidate any information on the time lag between lifestyle changes being made, weight loss occurring, and the observed reduction in risk of a shorter time to the combined endpoint following participation in the WMP. The study results may not be generalisable to the wider population of obese patients with CKD, as the study was conducted in a single urban centre. Additionally, the sustainability of the weight loss achieved after 12 months has not been explored in this study, although we have previously reported sustained weight loss up to 2 years in patients attending the WMP (MacLaughlin, Cook et al. 2010).

This study also has a number of strengths, particularly the robustness of the databases used to retrospectively collect data for the CON group, the use of a standardised, structured weight loss intervention delivered predominantly by a single experienced renal dietitian and a single experienced renal physiotherapist to the WMP group, and the continued observance of a significant relationship between the primary outcome and the WMP intervention even after accounting for potential confounding variables. The significant relationship between the combined outcomes of cardiovascular morbidity and all cause mortality, and participation in the WMP, remained significant when the analysis was repeated for all cause mortality alone, which removes any adjudication bias inherent in classifying cardiovascular disease events.

Participation in a structured weight management programme is associated with a reduction in the risk of a shorter time to the combined outcome of cardiovascular events and all cause mortality, yet has no impact upon the likelihood of kidney transplant waitlisting in obese patients with chronic kidney disease. Obese patients with CKD should be offered the opportunity to participate in a structured weight loss programme, given the probable association with cardiovascular protection demonstrated in this study. As the association evident in this observational study cannot be directly attributable to participation in the WMP, future research using adequately powered randomised controlled trials to determine the impact of weight reduction programmes on patient outcomes, including all cause mortality, cardiovascular morbidity and progression to end stage kidney disease, is warranted. In particular, further investigations to determine the impact of intentional weight loss treatments on survival in obese patients requiring haemodialysis treatment are recommended.

Chapter 3: Laparoscopic sleeve gastrectomy - a novel technique for weight loss in obese patients with chronic kidney disease

Chapter Summary

Obesity increases the risk of progression of chronic kidney disease (CKD) and kidney failure, and may preclude access to kidney transplantation. Weight loss surgery remains relatively novel in obese patients with CKD, with several studies reporting results using Roux-en-Y bypass and adjustable gastric banding; however, the safety of these techniques in obese patients with CKD is not certain, as kidney damage after bypass surgery and band erosion and migration after kidney transplantation have been reported in obese patients with CKD. This is the first study to describe the outcomes of the laparoscopic sleeve gastrectomy (LSG) technique in obese patients with CKD.

Weight loss, blood pressure, lipid profile, estimated kidney function, surgical complications, and adverse events were studied in the first 9 patients with CKD undergoing LSG from March 2007 to August 2010. Median excess BMI loss was 31% after 3 months and 49% after 6 months. 4/9 patients reduced anti-hypertensive medications. 4/5 patients on haemodialysis were added to the kidney transplantation waiting list after weight loss achieved post LSG. 3 adverse events occurred: myocardial infarction, acute kidney injury secondary to dehydration and compromised dialysis access. 1 patient also developed a gastric leak, detected 7 months after LSG, requiring further surgery and naso-jejunal feeding. Preliminary evidence suggests that sleeve gastrectomy is an effective treatment for obesity in patients with CKD. However, there may be additional risk associated with the procedure in patients with CKD, requiring further study.

Introduction

Obesity is associated with CKD progression and kidney failure, and whilst the exact mechanisms remain unknown, inflammation, dyslipidaemia, insulin resistance, and hypertension contribute to obesity related kidney damage (Becker, Kronenberg et al. 2005; Kramer, Luke et al. 2005; Hsu, McCulloch et al. 2006; Axelsson 2008; Teplan, Vyhnanek et al. 2010). Current practice guidelines for nutritional intervention in CKD provide very little guidance on the management of obesity in patients with CKD and the evidence is gleaned from epidemiological studies rather than clinical intervention trials (Fouque, Vennegoor et al. 2007; Holman, Paul et al. 2008; Wright and Jones 2010; Masoomi, Kim et al. 2011).

Sleeve gastrectomy is a relatively novel form of restrictive weight loss surgery in which a tube-like stomach is created after two-thirds subtotal gastric resection of the fundus and body (Figure 7), and is usually performed laparoscopically (ASMBS Clinical Issues Committee 2009).

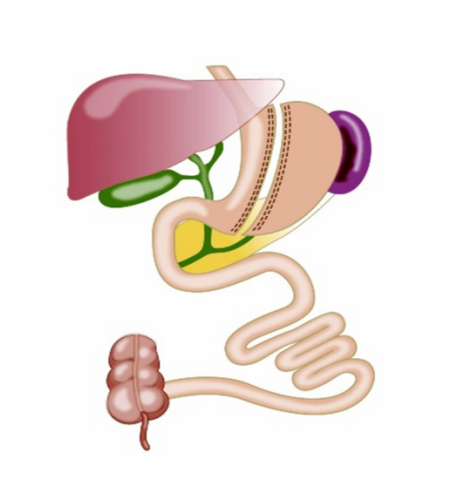


Figure 7: Diagram depicting sleeve gastrectomy

Obesity has been identified as a risk factor for the development and progression of CKD, yet well designed weight loss intervention studies are lacking. To date, studies on weight

loss surgery in obese patients with CKD have only examined gastric bypass and gastric banding surgical techniques, and detrimental effects related to the kidney have been reported with both procedures. LSG is emerging as a novel surgical operation for weight loss that is as effective as gastric bypass for weight loss and cardiovascular risk reduction (Benaiges, Goday et al. 2011), and is known not to be associated with nephrolithiasis, a recently apparent complication emerging as a barrier to performing gastric bypass in obese patients with CKD (Nelson, Houghton et al. 2005; Sinha, Collazo-Clavell et al. 2007; Nasr, D'Agati et al. 2008; Semins, Asplin et al. 2010) . Therefore, it appears reasonable to cautiously explore the use of LSG in the treatment of obesity in patients with CKD, initially with a small case series study of patients electing to undergo LSG and to report on observed weight loss and complications, with a view to conducting a set of prospective, controlled, intervention studies in this population.

Study Aim

To date, the safety and effectiveness of sleeve gastrectomy for the treatment of obesity in patients with CKD has not been reported in the literature. This study aims to describe the first case-series of obese patients with CKD undergoing sleeve gastrectomy, performed in a single centre in the United Kingdom. The study reports on the extent of weight loss achieved, and documents the surgical complications and post-operative adverse events over the observation period.

Hypothesis

Laparoscopic sleeve gastrectomy in obese patients with CKD results in weight loss equivalent to that reported in the literature for other patient groups undergoing this treatment for obesity.

Methods

In order to provide evidence on the efficacy and safety of the LSG in obese patients with CKD, prior to the conduction of planned controlled intervention studies, a retrospective review of written and electronic medical records for consecutive patients with CKD, under the care of a nephrologist, who underwent LSG for weight loss between March 2007 and August 2010 at King's College Hospital, London, was conducted. All patients under the care of a nephrologist at King's College Hospital have records of clinic visits, hospital admission, results of investigations and letters to other medical professionals stored on two electronic databases. Prospective dietetic care records were kept for all patients and the databases were searched for the predetermined information from dietetic records, and records of routine surgical or nephrology appointments. The study was classified as audit and therefore deemed not to require full ethical review and was approved by the King's College Hospital Research Ethics Committee.

The pre-specified measures selected to be examined were peri-operative length of hospital stay, post operative inflammatory response (C-reactive protein), all post surgical complications, weight loss, BP, triglycerides, and serum cholesterol, antihypertensive and lipid lowering medication changes, eGFR using the 4 variable Modification of Diet in Renal Disease Study equation in patients in stages 1-4 CKD (Levey, Bosch et al. 1999; Levey, Greene et al. 2000), kidney transplantation wait-listing, and all adverse events occurring during the follow-up period. Complications may include gastrectomy leak, bleeding requiring transfusion or invasive intervention, and 30-day mortality. Possible adverse events included compromised dialysis access, cardiovascular events including myocardial infarction, cardiac arrhythmia and stroke, acute kidney injury and re-hospitalisation during the study period. Data collection was completed between December 2010 and March 2011.

Weight loss measures are defined in Table 7.

Table 7: Definitions of weight loss parameters to define weight loss in patients undergoing laparoscopic sleeve gastrectomy

Parameter	Definition
Absolute weight loss (kg)	Body weight at baseline (kg) - body weight at defined time point (kg)
% Weight loss	[Absolute weight loss (kg)/body weight at baseline (kg)] x 100
% Excess BMI loss	[Absolute weight loss/difference between baseline BMI and BMI = 25 kg/m^2] x 100
% Excess weight loss	[Absolute weight loss/difference between baseline weight and the mid point of the 1983 Metropolitan Life Insurance Tables for medium build)] x 100 (Deitel, Gawdat et al. 2007)

BMI – body mass index (weight (kg)/height (m)^2)

All patients underwent a routine pre-operative evaluation prior to surgery. This assessment included an evaluation of medical history, potential contraindications to surgery including individual patient anaesthetic risk, cardiac risk, wound healing risk secondary to diabetes or blood disorders, as well as outlining the known risks and benefits of the procedure in obese patients who do not have CKD. Patients were provided with written information on the procedure and were given the opportunity to ask questions.

A single experienced surgeon performed the LSG in all patients. 6 trocars were utilised and LSG was performed with standard techniques using a 38 French bougie. After devascularisation of the greater curvature, the sleeve gastrectomy commenced 4 - 6 cm proximal to the pylorus on the greater curvature and continued towards the angle of His. The completed staple line was reinforced with sutures. Post operatively, all patients received anti-coagulation therapy and wore compression stockings for embolism prophylaxis. Within 3 – 6 days post-operatively, gastrografin meal and follow-through analyses were performed for all patients to observe pyloric emptying function and methylene blue dye tests were carried out on patients with post-operative drains in situ to detect gastric leak.

Post-operative dietary education was provided by dietitians experienced in the dietary management of either weight loss surgery or CKD, but not both, due to the novelty of this procedure in patients with CKD. Post operative diet consisted of fluids only for 4 weeks, pureed consistency foods for a further 2 - 4 weeks, followed by soft foods for an additional 4 weeks, then the gradual return to normal foods in reduced portions. Consumption of at least 2 litres of fluid per day was encouraged for patients with CKD not on dialysis. Appropriate fluid and intake and electrolyte management was incorporated into the dietary education for patients on dialysis on an individual basis due to varying levels of urine output and very limited kidney function in these patients.

Protein and energy requirements were estimated for all patients and dietary education was individualised to meet these requirements. Energy requirement was set at between 1 000 - 1 200 kcal per day for all patients, to induce weight loss, induce satiety and to ensure that food intake did not exert excess pressure on the newly formed stomach staple line (Snyder-Marlow, Taylor et al. 2010). Protein requirement was established using the NKF-KDOQI guidelines of 0.75 g/kg ideal body weight (weight at BMI = 25)/day for patients with stage 4 CKD (estimated kidney function of 15 – 29 ml/min/1.73m^2) and 1.2 g/kg ideal body weight (weight at BMI = 25)/day for patients on dialysis (2000). Patient in stages 1-3 CKD were encouraged to have a normal protein intake and not to exceed 1.3 g protein/kg body weight/day (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). High protein liquid nutritional supplement drinks or specialist renal protein powder supplements were prescribed for dialysis patients to enable them to meet protein requirements within an energy, fluid and electrolyte restricted diet. All patients received renal specific, written information on suitable foods and textures for each stage of the modified diet, together with suggested meal plans (Appendix A).

Results

9 patients (3 Male; 6 Female) with CKD, median age 44.0 years, median weight 118.0 kg and median BMI 44.2 kg/m^2 underwent LSG for treatment of obesity. Baseline demographic and peri-operative data for all patients are listed in Table 8. 5 patients had stage 5 CKD and were undergoing chronic haemodialysis. At the time of surgery, median dialysis vintage was 18 months (range 11 - 106 months). 4 patients were in stages 1-4 CKD, with a baseline eGFR between 18 - 110 ml/min/1.73m^2. In this series, Patient J underwent a re-sleeve gastrectomy, after an initial procedure with a larger sleeve was performed 3.5 years earlier in another centre, and significant weight re-gain had occurred. Patients were followed up for between 6 - 39 months, with a median follow up period of 9 months.

Table 8: Baseline demographic and peri-operative data for 9 obese patients with chronic kidney disease who underwent laparoscopic sleeve gastrectomy for weight loss

Patient	Age	Sex	CKD stage	Estimated kidney function	CKD cause	DM	Weight (kg)	BMI (kg/m^2)	LOS (days)
A	44	F	3	40%	Porphyria	no	147.3	49.8	9
B	38	F	1	100%, with proteinuria	FSGS	no	118.6	46.3	4
C	39	M	5-HD	-	FSGS	no	125.0	41.8	16
D	41	F	5-HD	-	APKD/DM	yes	129.0	47.4	6
E	53	F	5-HD	-	DM	yes	113.0	36.5	10
F	41	M	5-HD	-	HT	no	114.0	33.3	9
G	48	M	5-HD	-	HT	no	140.0	44.2	9
H	51	F	4	18%	IgA	no	99.0	43.0	8
J	60	F	2	65%	HT/Obesity	no	117.1	46.3	6

CKD stage: chronic kidney disease stage using KDIGO classification; DM: diabetes; BMI: body mass index (weight (kg)/height (m)^2); LOS: peri-operative length of stay in hospital; HD: haemodialysis; FSGS: focal segmental glomerulosclerosis; AKPD: adult polycystic kidney disease; HT: hypertension; IgA: Immunoglobulin A nephropathy

Median length of peri-operative hospital stay was 9 days (range 4 - 16 days). Patient A was admitted to critical care for < 48 hours post operatively, with reduced kidney function on day 1 post-operatively, which recovered on day 2, and patient C required high dependency care post-operatively due to a chest infection. Gastrografin meal and follow through reports were negative for gastric leak in all patients, and delayed stomach emptying was observed in patient G.

C-reactive protein level rose in the immediate post operative period in all patients, peaked at days 4 to 7, but settled back to baseline level by three months. eGFR fell in 3/4 patients in stages 1-4 CKD at day 1-2 post-operatively, but returned to baseline prior to discharge in all patients.

There was no 30-day or overall mortality in this case series. One surgical complication was evident in a single patient post-operatively. Patient E, on haemodialysis, had a normal gastrograffin follow-through and methylene blue dye test prior to discharge. Ongoing investigations of a persistently low haemoglobin level that was unresponsive to recombinant erythropoietin treatment led to detection of, initially, diverticulitis, and latterly, a small gastric leak associated with a subphrenic collection 7 months post-operatively. Patient E underwent two further surgical procedures requiring general anaesthesia, involving evacuation of the collection, stenting, and re-stenting of the leak via laparoscopy. Whilst the leak healed full nutrition was provided with enteral nutrition support with naso-jejunal feeding for 7 weeks, and then a further 12 weeks after an unsuccessful trial of oral intake.

Minor adverse events occurred in 2 of 9 patients, in patient F dialysis access was compromised by fistula thrombosis on day 1 post-operatively, requiring angioplasty and stenting on day 4 to re-establish permanent dialysis access. Patient H experienced acute kidney injury secondary to dehydration 2 weeks post-operatively, requiring hopsitalisation and intravenous re-hydration. Kidney function, in patient H, remained below baseline for 2 months but returned to baseline after 3 months.

One major adverse event occurred during the study period. Patient E displayed non-symptomatic significant electrocardiogram changes 3 weeks post-operatively suggestive of

myocardial infarction with non-Q wave coronary occlusion. Subsequent angiography showed obstruction of the left anterior descending artery, requiring angioplasty and stenting.

Weight loss parameters for each patient, and median weight loss, at 3 and 6 months following sleeve gastrectomy are presented in Table 9. Median excess weight loss at 6 months was 43.0% (range 31.2 - 53.6%). Figure 8 displays the rate of % excess weight loss up to 1 year for each patient. The rate of weight loss slowed after 3 months in all but patient B, who continued with a constant rate of weight loss for 6 months.

Table 9: Weight loss parameters 3 and 6 months post laparoscopic sleeve gastrectomy in obese patients with chronic kidney disease

Patient	Absolute weight loss (kg)		% Weight loss		% Excess weight loss		% Excess BMI loss	
	months post SG		**months post SG**		**months post SG**		**months post SG**	
	3	**6**	**3**	**6**	**3**	**6**	**3**	**6**
A	21.1	25.7	14.3	17.4	25.6	31.2	28.8	35.0
B	16.6	32.3	14.0	27.2	27.6	53.6	30.4	59.2
C	21.0	25.0	16.8	20.0	37.2	44.3	41.9	49.8
D	24.6	30.0	19.1	23.3	36.2	44.2	40.4	49.2
E	14.0	19.8	12.4	17.5	30.4	43.0	39.4	55.7
F	14.0	14.0	12.3	12.3	35.9	35.9	49.2	49.2
G	19.0	24.5	13.6	17.5	27.6	35.6	31.3	40.3
H	13.1	21.0	13.2	21.2	28.5	45.7	30.6	49.1
J	15.3	19.1	13.1	16.3	25.8	32.2	28.4	35.4
median	16.6	24.5	13.6	17.5	28.5	43.0	31.3	49.2

SG – laparoscopic sleeve gastrectomy surgery for weight loss; % excess weight loss = [absolute weight loss/(baseline weight – ideal weight using mid point of 1983 Metropolitan Life Insurance Tables for medium frame)] x 100 (Deitel, Gawdat et al. 2007); BMI – body mass index [weight (kg)/height (m)^2]; % excess BMI loss = [absolute change in BMI/(baseline BMI – 25)] x 100

Median systolic BP decreased from 136 mm Hg to 126 mm Hg after 3 months, and there was no change in median diastolic BP. Antihypertensive agents were reduced in 3/7 patients on anti-hypertensive therapy, ceased in 1/7 patients and were unchanged in the remaining 3 patients. Median serum cholesterol decreased from 5.5 mmol/L to 4.6 mmol/L and medium triglycerides did not change after 3 months. 3 patients were on

statin therapy for lipid lowering at baseline, which was ceased in 1 patient, and remained unchanged in 2 patients.

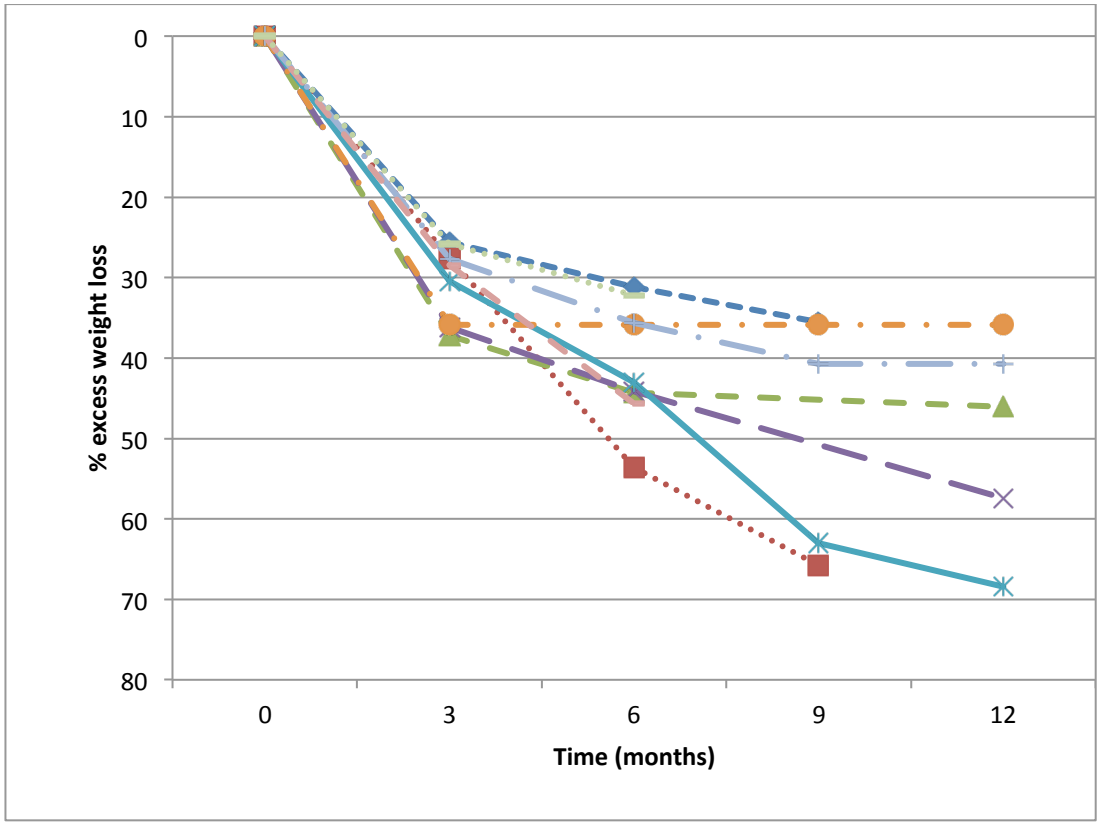


Figure 8: % excess weight loss* after laparoscopic sleeve gastrectomy in 9 obese patients with chronic kidney disease

*% excess weight loss = [absolute weight loss/(baseline weight – ideal weight using mid point of 1983 Metropolitan Life Insurance Tables for medium frame)] x 100

Of the 2 out of 9 patients with diabetes, only patient E was on insulin therapy. The insulin dose was decreased from 50 to 38 units/day within 1 month of sleeve gastrectomy, and HbA1c improved from 9.0% to 6.1% after 6 months.

Hyperfiltration decreased in patient A, the only patient with hyperfiltration at baseline, but there was no change in estimated kidney function in any other patient following weight loss after 6 months.

Of the 5 patients on haemodialysis, patients C, D, E and F were listed for kidney transplantation over the study period, at 4, 5, 10 and 12 months post LSG respectively.

Patient E was then suspended from the kidney transplantation waiting list 2 weeks after being listed, due to infection and then remained suspended following the diagnosis of gastric leak and subphrenic collection. At the time of writing, Patient G had not yet been listed for kidney transplantation, as weight remained above the target BMI established by the transplant surgeon, 12 months after LSG.

Discussion

This is the first study to describe the weight loss achieved, adverse events and complications after LSG in obese patients with CKD. After 6 months excess BMI decreased by 49.2% and excess body weight was reduced by 43.0%. Systolic BP and serum cholesterol decreased, and anti-hypertensive and lipid lowering medications were reduced in some patients. There was no mortality, one major surgical complication and 3 adverse events in this series. This is the first study to support the use of LSG as an efficacious treatment for obesity in CKD.

A systematic review of weight loss after sleeve gastrectomy in the general population indicates that excess body weight loss is between 36–85%, after a follow-up period of 3–60 months, including excess weight loss of 35–59% after 6 months (Brethauer, Hammel et al. 2009). As the median excess weight loss in this series was 43% after 6 months, this suggests that the weight loss achieved in patients with CKD is similar to that achieved in patients without CKD who have undergone the same weight loss procedure. Longer-term follow up is required to determine whether weight loss is maintained over time.

The rate of weight loss in this series began to differ between patients 3 months post-operatively, once dietary restriction of all solid foods was no longer necessary. Differences in the rate of weight loss between patients became apparent once a larger variety of foods,

differing textures and quantities began to be tolerated, indicating that patients may still influence their individual degree of weight loss by their chosen food intake, which affects total energy intake. The importance of considering the total weight loss in the context of the starting BMI is highlighted in this series by patient F, who still achieved a reduction in excess BMI of 49% despite no further weight loss after three months, due to a lower starting BMI than the rest of the patients in the series.

Hyperfiltration decreased in one patient, and there was no change in eGFR after 6 months in the other 8 patients in this series. eGFR is calculated using serum creatinine, which may fall as body size decreases if muscle mass is reduced as well as fat mass, therefore an improvement in eGFR with a reduction in muscle mass with weight loss may be expected (Delanaye, Radermecker et al. 2005). Some studies of Roux-en-Y gastric bypass surgery and laparoscopic adjustable gastric banding demonstrate an improvement in eGFR after 6 and 12 months (Alexander, Goodman et al. 2009; Navaneethan and Yehnert 2009).

1 patient experienced major complications with a late detected gastric leak. The same patient also required angioplasty and stenting of the left anterior descending artery after myocardial infarction detected 3 weeks post-operatively. 2 other adverse events occurred, although it is not possible to ascertain whether the occlusion of the arteriovenous fistula was related to the weight loss surgery or not. There was no post-operative bleeding reported in this series and no evidence of nephrolithiasis or oxalate nephropathy – although this would not be expected in a restrictive procedure. In the general obese population, a systematic review suggests major complications occur in 0 - 15.3% of patients post sleeve gastrectomy (Brethauer, Hammel et al. 2009). Whilst it is not appropriate to extrapolate the complication rate in patients with CKD from the 9 patients in this series, as there were 3 complications and 1 major adverse event reported in a series of 9 patients, it is

reasonable to conclude that complications, and possibly unrelated events may be higher in obese patients with CKD than in the general population. As patients with CKD demonstrate a higher risk of cardiovascular disease than the general population (Sarnak, Levey et al. 2003; Go, Chertow et al. 2004), this poorer vascular health in patients with CKD may impact upon healing, wound stabilisation and the cardiovascular event rate observed during the study. Whilst a sub-analysis of 37 patients with ischaemic heart disease included in the Swedish Obese Subjects (SOS) study found no greater peri-operative complication rate compared to obese patients without cardiovascular disease (Delling, Karason et al. 2010), recent large observational studies indicate that patients with CKD have a higher risk of complications post-operatively for all types of non-emergency surgery, and the risk of complications with weight loss surgery increases with higher stages of CKD (Nguyen, Masoomi et al. 2011; Turgeon, Perez et al. 2012). Both the small sample size and the types of operations in the SOS study participants, which were predominantly the minimally invasive gastric banding or the now rarely performed vertical banded gastroplasty, both of which are lower risk operations than sleeve gastrectomy or gastric bypass, are limitations of the study and as it did not include patients with pre-existing CKD the results may not be applicable to CKD populations.

Similarly, the likelihood of gastric leak following gastric bypass surgery is increased in patients with chronic renal failure (adjusted odds ratio 2.38), compared to patients without renal failure, although incidence of gastric leak was not affected by hypertension, hyperlipidaemia, diabetes, peripheral vascular disease or smoking (Masoomi, Kim et al. 2011). Whilst the surgical procedure differs, the risk of leak similar in all forms of weight loss surgery (Picot, Jones et al. 2009). Therefore, the occurrence of gastric leak in this series would not be entirely unexpected, although the delayed detection of the leak is unusual. Interestingly, patient E became anaemic prior to the detection of the gastric leak;

other causes of anaemia were investigated initially, yet anaemia may be an early sign of leak or bleeding post weight loss surgery.

The importance of adequate hydration during rapid weight loss (Snyder-Marlow, Taylor et al. 2010), even in patients with impaired or depleted kidney function with reduced urine output, remains apparent, with 2 of 3 adverse events in this series likely related to inadequate hydration post-operatively, despite the use of intravenous fluids post-operatively and provision of patient education on goal oral fluid intake after discharge. Four out of 5 patients on dialysis were listed for kidney transplantation within 12 months following weight loss achieved after LSG. As the mean waiting time for kidney transplantation is now over 2 years, it remains too early to report on successful kidney transplantation in this series of patients. Reductions in antihypertensive and lipid-lowering medications indicate that other factors associated with obesity may also be reduced in obese patients with CKD following weight loss surgery with LSG.

This study is limited by its small sample size, and lack of control or comparison group. Safety of the LSG procedure for weight loss in obese patients with CKD cannot be determined from this case series. Indeed, several large controlled trials or retrospective analyses of large databases will be required to establish the safety and risks of the procedure in obese patients with CKD. Since the conception of this study it is now known that the risk of complications and mortality with other forms of weight loss surgery are increased in patients with CKD (Nguyen, Masoomi et al. 2011; Turgeon, Perez et al. 2012). Therefore it is highly likely that the risk of complications and mortality may also be increased with the LSG procedure for weight loss in obese patients with CKD compared to obese patients without CKD.

In conclusion, this is the first study to describe the early course of obese patients with CKD electing to undergo LSG, in a single centre. LSG appears to be a reasonable option to consider in the treatment of obesity in patients with CKD, particularly with a view to improving access to kidney transplantation waitlisting. However, the procedure may carry a higher rate of complications and adverse events in patients with CKD than in those without CKD, so careful monitoring of fluid intake, kidney function and dialysis access is required, together with clear patient education on the importance of compliance to the post-operative diet. Larger prospective controlled studies of LSG in obese patients with CKD are clearly needed to provide further evidence on the safety and effectiveness of this procedure in the treatment of obesity in patients with CKD.

Chapter 4: A prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in obese patients on haemodialysis - pilot study

Chapter Summary

One third of patients undergoing haemodialysis treatment die from complications related to cardiovascular disease, and kidney transplantation is the only effective treatment option to reduce mortality. Obesity may restrict access to kidney transplantation, as many transplantation centres limit access to kidney transplants to patients with a body mass index (BMI) < 35 kg/m^2. Laparoscopic sleeve gastrectomy (LSG) is a relatively novel, restrictive, surgical weight loss procedure performed to reduce the size of the stomach by two-thirds, thereby limiting food intake. Prior to our studies, there have been no reports of LSG as a weight loss treatment in patients with chronic kidney disease (CKD). This prospective cohort pilot study aimed to evaluate the efficacy of LSG surgery in obese patients with kidney failure currently undergoing haemodialysis, as a strategy to increase eligibility for kidney transplantation. The secondary aims of the study were to monitor surgical complications and adverse events, and the effect of weight loss on quality of life, insulin resistance, hypertension and dyslipidaemia. Additionally, several cardiovascular disease risk biomarkers, including assessment of arterial stiffness with brachial-femoral pulse wave velocity (PWV) and measurement of the number and function of endothelial progenitor cells (EPC) were undertaken to determine the feasibility of using these measures in a larger trial. The planned sample size for this study was 15 subjects undergoing surgery, with a similar-sized comparator group consisting of matched patients who did not undergo surgery. Part way through this investigation, study approval was withdrawn by the host site, after 2 serious adverse events were reported. 18 patients were recruited prior to early suspension of the study. 6 patients in the LSG group were matched for age and gender with 6 patients electing to maintain usual care (UC), and a further 6 patients were recruited

to the LSG group but had yet to undergo baseline assessment prior to study suspension. Four patients underwent LSG before the study was suspended. There were 2 serious adverse events, including 1 death post-operatively, and the host site suspended the study approval. All 3 surviving patients in the LSG group reduced their weight to reach a target BMI < 35 kg/m^2 and all 3 became eligible for kidney transplantation 3 months after weight loss surgery. There were no adverse events in the UC group. A further 2 patients allocated to the LSG group died prior to baseline assessment. The mortality in this study concurs with the known mortality rate in patients with kidney failure undergoing haemodialysis. The safety and efficacy of LSG in this patient group could not be determined, as the study was terminated prior to completion.

Introduction

There is little evidence informing clinical practice on the role of weight loss surgery for obese patients undergoing haemodialysis as treatment for kidney failure. 2 case reports (Knerr, Horbach et al. 2003; Holman, Paul et al. 2008; Tafti, Haghdoost et al. 2009) and 4 small case series (Newcombe, Blanch et al. 2005; Koshy, Coombes et al. 2008; Takata, Campos et al. 2008; Alexander, Goodman et al. 2009) suggest that weight loss surgery may be beneficial in obese patients on haemodialysis to improve candidacy for kidney transplantation (Newcombe, Blanch et al. 2005; Koshy, Coombes et al. 2008; Takata, Campos et al. 2008), promote recovery of kidney function (Alexander, Goodman et al. 2009; Tafti, Haghdoost et al. 2009) or improve viability of dialysis vascular access (Knerr, Horbach et al. 2003). However, both laparoscopic gastric banding and gastric bypass surgery have been associated with negative effects on the kidney in a minority of patients (Nelson, Houghton et al. 2005; Buch, El-Sabrout et al. 2006; Sinha, Collazo-Clavell et al. 2007; Nasr, D'Agati et al. 2008).

Chapter 3 detailed the results of using LSG as a novel treatment for weight loss in obese patients with CKD. The case series included 5 patients undergoing haemodialysis. Significant weight loss was achieved, and 4 out of the 5 haemodialysis patients became eligible for kidney transplantation waitlisting. However, one haemodialysis patient's dialysis vascular access failed, and another patient experienced a myocardial infarction and gastric leak post LSG weight loss surgery. The case series indicated that whilst LSG may be efficacious for weight loss and improve candidacy for kidney transplantation, there may be additional risks associated with the procedure in patients with CKD, indicating a need for an exploratory, yet systematic, prospective observational study of LSG for weight loss in obese patients undergoing haemodialysis.

This chapter describes a prospective, observational, cohort pilot study of LSG, compared to usual care, in haemodialysis patients only, to determine the efficacy of the surgery for enabling the patient to achieve a BMI below the threshold acceptable for kidney transplantation in the study centre. Secondly, this study aimed to monitor the safety of LSG in patients on haemodialysis, and to determine the effect on quality of life.

Research Question: In obese patients with kidney failure on haemodialysis, is weight loss achieved with laparoscopic sleeve gastrectomy adequate to enable patients to meet kidney transplant waitlisting criteria?

Study Aim

This study aimed to evaluate the efficacy of the sleeve gastrectomy procedure to elicit sufficient weight loss to enable kidney transplantation in obese patients with kidney failure currently undergoing haemodialysis. Additionally, the efficacy of the procedure for

improving quality of life, reducing insulin resistance, hypertension and dyslipidaemia was studied, and adverse effects were monitored. Furthermore, this study intended to measure changes in selected cardiovascular biomarkers to determine the effect size attributable to weight loss and assess the practicality of these measurements in preparation for use in a future randomised controlled trial.

Primary Hypothesis

Obese haemodialysis patients with a body mass index of > 35 kg/m^2 undergoing laparoscopic sleeve gastrectomy will reduce weight sufficiently to meet the kidney transplantation criteria of body mass index < 35 kg/m^2 after 12 months, compared to those continuing best medical care.

Primary outcome

The primary outcome measure was weight loss and achievement of kidney transplantation listing body mass index criteria of BMI < 35 kg/m^2 12 months post laparoscopic sleeve gastrectomy, compared to best medical care.

Secondary Hypotheses

The following hypotheses and outcomes were selected, as they are patient-focused outcome measures. Other clinical and metabolic outcomes have been classified as exploratory outcomes.

Secondary Outcomes

1. **Quality of life (Self Adminstered Short Form 36 and Hospital Anxiety and Depression Scale) scores improve following laparoscopic sleeve gastrectomy, compared to best medical care.**

The self adminstered Short Form 36 (SF-36) is a widely used quality of life measurement tool assessing physical and mental health domains. The tool measures eight dimensions of quality of life, with general health and vitality contributing to both the physical and mental domain scores, and physical functioning, role physical and pain also incorporated into the physical domain and social functioning, role-emotional and mental health into the mental domain score (Lacson, Xu et al. 2010). Domain scores range from 0 to 100, with a higher score representing better self-reported health. SF-36 scores are reduced in patients with CKD compared to healthy controls, and continue to decline as CKD progresses (Perlman, Finkelstein et al. 2005). In haemodialysis patients, SF-36 score has inverse relationships with BMI, body fat level, and mortality (Kalantar-Zadeh, Kopple et al. 2001; Lowrie, Curtin et al. 2003). Weight loss surgery is associated with improved quality of life in most, but not all studied populations (Ballantyne 2003).

The Hospital Anxiety and Depression Scale (HADS) was developed as a self administered screening tool to detect anxiety and depression in hospitalised patients (Zigmond and Snaith 1983). HADS scores for both the anxiety and depression scales have been demonstrated to decrease from high to normal values with weight loss following weight loss surgery after 1 and 2 years (Andersen, Aasprang et al. 2010). Quality of life is important to measure to aid in future clinical treatment decisions. If quality of life improves with weight loss, regardless of other outcome measures, the intervention treatment may be worth pursuing for perceived patient benefit alone.

2. **Weight loss following laparoscopic sleeve gastrectomy resolves or improves insulin resistance, hypertension and dyslipidaemia, compared to best medical care.**

Insulin resistance, hypertension and dyslipidaemia are elements of metabolic syndrome, which is associated with both CKD and obesity (Wahba and Mak 2007; Sarafidis 2008). Weight loss in obese patients without CKD is known to improve all three elements (Klein 2001; Bougoulia, Triantos et al. 2006), yet there is little information on the effect of weight loss on these parameters in obese patients with CKD. Additionally, hyperglycaemia, hypertension and dyslipidaemia are largely managed with drug therapy in the dialysis population and the additional effect of weight loss, if any, is largely unknown. HOMA-IR is a robust indirect indicator of insulin resistance (Matthews, Hosker et al. 1985), which has been demonstrated to increase with obesity in patients with CKD (Axelsson, Bergsten et al. 2006), and is associated with cardiovascular mortality in patients undergoing haemodialysis (Shinohara, Shoji et al. 2002). It is expected that an improvement in insulin resistance with weight loss may be associated with changes in inflammatory markers, body fat, body weight, waist circumference and/or adiponectin. A reduction in systolic BP and an increase in HDL cholesterol has been demonstrated following weight loss surgery in patients without CKD (Martins, Strømmen et al. 2011), although systolic BP and lipid measures are not related to BMI in patients undergoing dialysis (Bossola, Giungi et al. 2008).

3. **The complication rate for laparoscopic sleeve gastrectomy is no greater in obese haemodialysis patients than in non-dialysis patients undergoing the same procedure.**

Typical complications related to LSG weight loss surgery include gastrectomy leak, bleeding requiring transfusion, bleeding or restriction requiring surgical or endoscopic intervention. The additional effect of heamodialysis on the complication rate is not yet known.

4. **The adverse event rate over 12 months is no greater in obese haemodialysis patients undergoing laparoscopic sleeve gastrectomy than in obese patients on haemodialysis continuing with best medical care.**

Adverse events may include malnutrition, dehydration, vomiting, hypoglycaemia, constipation, epigastric pain, oedema, and cardiovascular events - including myocardial infarction, stroke and hospitalisation for heart failure. This patient population has an elevated risk of cardiovascular events and malnutrition, and it is predicted that weight loss following LSG may reduce the incidence of adverse events in this group. Malnutrition was assessed with the Subjective Global Assessment (SGA) nutrition assessment tool, validated for use in haemodialysis patients (Steiber, Leon et al. 2007).

Additionally, this pilot study had a pre-defined a range of exploratory outcome measures selected in order to determine practicality of measurement, as well as effect size and direction in preparation for a future planned randomised controlled trial of LSG in obese patients on haemodialysis.

The exploratory outcome measures were:

Waist circumference and waist to hip ratio

Waist to hip ratio is related to cardiovascular disease risk (myocardial infarction (MI) and fatal coronary disease) in patients with CKD (Elsayed, Tighiouart et al. 2008) and waist circumference and waist to hip ratio provide alternative measures of body fat distribution to BMI.

Obesity related inflammatory or anti-inflammatory factors: Fetuin-A, CRP, IL-6, TNF-alpha, leptin and adiponectin

Leptin levels are associated with subcutaneous adipose tissue and adiponectin is associated with visceral adipose tissue in haemodialysis patients (Kaysen, Kotanko et al. 2009). Neither IL-6 nor TNF-α are associated with measures of fat mass or lean body mass in haemodialysis patients, indicating that the haemodialysis inflammatory state overrides other factors influencing inflammation evident in non-dialysis populations (Beberashvili, Sinuani et al. 2009), although the effect of weight loss on these relationships has not been assessed in obese patients on haemodialysis. Fetuin-A is a peptide secreted exclusively by the liver, and it is a potent inhibitor of vascular calcification. Fetuin-A also impairs insulin signalling, and is associated with metabolic syndrome in patients with CKD (Ix, Chertow et al. 2006; Axelsson, Wang et al. 2008; Ix and Sharma 2010). Fetuin-A is increased in obesity and is associated with survival in dialysis patients (Hermans, Brandenburg et al. 2007).

Arterial stiffness (aortic pulse wave velocity)

Arterial stiffness is measured by carotid to femoral, and brachial to femoral, pulse wave velocity (PWV), by recording arterial pulse waveforms with a device such as the Vicorder oscillometric device (Skidmore Medical: United Kingdom). Increased PWV, indicating increased aortic stiffness, is associated with measures of obesity, although the mechanism linking adiposity to aortic stiffness is not well defined (Safar, Czernichow et al. 2006). The Vicorder, which measures both carotid to femoral PWV, and brachial to femoral PWV, has been validated against the recognised gold standard SphygmoCor system, which measures carotid to femoral PWV (Hickson, Butlin et al. 2009), and PWV is predictive of survival in haemodialysis patients (Morimoto, Yurugi et al. 2009). Pulse wave velocity is also an independent predictor of cardiovascular events in patients with stages 4-5 CKD, even after adjustment for established cardiovascular risk factors (Zoungas, Cameron et al. 2007).

Reductions in arterial stiffness with therapeutic interventions, such as weight loss, represent a true reduction in arterial wall damage, rather than simply a change in cardiovascular risk scores achieved with reductions in hypertension, lipid lowering and improvement in glycaemic control (Laurent, Cockcroft et al. 2006).

Endothelial progenitor cells (EPC)

EPC are required for regeneration and repair of vascular tissue, and a reduction in EPC number and/or function has been demonstrated independently in CKD, end stage kidney disease, and obesity (Choi, Kim et al. 2004; de Groot, Bahlmann et al. 2004; Herbrig, Pistrosch et al. 2006; Muller-Ehmsen, Braun et al. 2008; Jourde-Chiche, Dou et al. 2009; Krenning, Dankers et al. 2009; MacEneaney, Kushner et al. 2009; Bahlmann, Speer et al. 2010; Buemi, Costa et al. 2010; Heida, Müller et al. 2010; Jie, Zaikova et al. 2010).

Intentional weight loss in overweight and obese subjects, without overt kidney disease, is linked to improvement in endothelial function (Pierce, Beske et al. 2008), an increase in number and functionality of EPC (Muller-Ehmsen, Braun et al. 2008; Heida, Müller et al. 2010), and reduced CRP (Esposito, Pontillo et al. 2003). There are no data available on the effect of weight loss on EPC in obese haemodialysis patients. This information may help to determine whether weight loss reduces the inflammatory assault and increases the efficacy and number of EPC, which, in turn, may improve vascular function and reduce cardiovascular disease morbidity.

Various methodologies have been used previously, as no unique cell surface marker/s of EPC have been identified, and all studies in haemodialysis patients have included only small numbers of patients (Krieter, Fischer et al. 2010). The Colony Forming Unit-Hill (CFU-Hill) method of culturing EPC colonies, appears to be associated with EPC function,

and was chosen due to its association with Framingham risk score in apparently healthy men (Hill, Zalos et al. 2003).

The cell surface markers CD34+/CD133+/KDR+ were selected, since various combinations of these have been used to detect EPC in peripheral blood mononuclear cells (PBMC) in obesity and CKD separately, however no existing data could be found on EPC counts for obese patients with CKD (Jourde-Chiche, Dou et al. 2009; Heida, Müller et al. 2010). CD 34+/CD 133+/KDR+ and CD34+/KDR+ and CD133+/KDR+ cell counts negatively correlate with BMI (Tobler, Freudenthaler et al. 2010), but there was no relationship between CD34+/CD133+ and BMI, and leptin is negatively correlated with all individual markers and combinations.

Reduction in EPC number and/or function has been demonstrated independently in CKD, end stage kidney disease, and obesity (Choi, Kim et al. 2004; de Groot, Bahlmann et al. 2004; Herbrig, Pistrosch et al. 2006; Jourde-Chiche, Dou et al. 2009; Krenning, Dankers et al. 2009; MacEneaney, Kushner et al. 2009; Bahlmann, Speer et al. 2010; Buemi, Costa et al. 2010; Heida, Müller et al. 2010; Jie, Zaikova et al. 2010), which may contribute to deterioration of endothelial function. Weight loss in obese patients without CKD results in improvement in number and functionality of EPC (Muller-Ehmsen, Braun et al. 2008; Heida, Müller et al. 2010). It is hypothesised that weight reduction will lead to an increase in EPC in obese patients on haemodialysis, which may contribute to an improvement in vascular function and reduction in cardiovascular risk.

Methods

Study Design

This study was an observational cohort study of obese haemodialysis patients who self selected to accept or decline LSG weight loss surgery (Figure 9).

Ethical Review and Research Governance

This study followed the principles of the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (World Medical Association 2008), and was submitted to the West London Research Ethics Committee in March 2010. The committee did not give a favourable opinion for the study, due to differences between the study protocol and the Integrated Research Application System (IRAS) project information submitted for ethical review. Significant amendments were made to the study protocol and the IRAS project information. The study was then submitted to the Queen Square Research Ethics Committee in June 2010 and approved in October 2010, after further information was provided and amendments made to the written Information for Participants booklet (Appendix C) highlighting the unknown risk of LSG surgery in patients with CKD and informing the patient that undergoing weight loss surgery did not guarantee kidney transplant waitlisting. King's College Hospital Research and Development governance approval was granted in January 2011, followed by approval from St Helier Hospital and Guy's and St Thomas' Hospital soon afterwards.

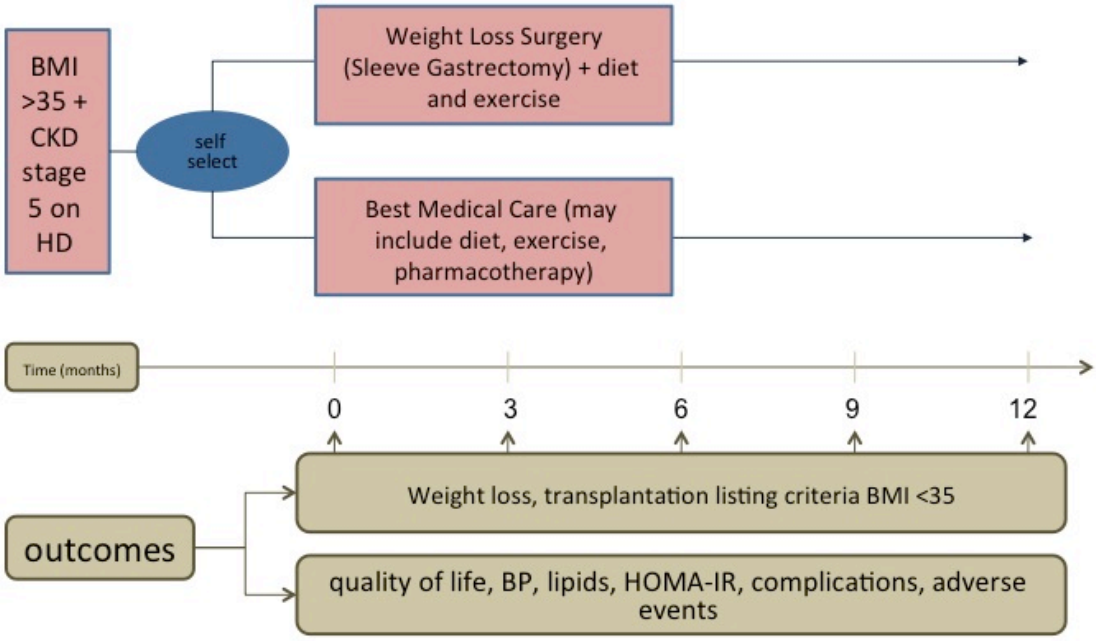


Figure 9: Schematic representation of study design and outcomes
BMI – body mass index; CKD – chronic kidney disease; BP – blood pressure; HOMA-IR – method of homeostasis assessment for insulin resistance

Recruitment of patients

Recruitment commenced in January 2011 and ceased in December 2011, when the study was terminated early. Patients were recruited from haemodialysis centres attached to the 3 study sites.

Preliminary Screening

Screening existing patient databases and patient medical records at haemodialysis centres linked to the 3 study sites identified potential patients. A member of the site clinical care team completed screening in conjunction with the candidate. Screening was based on the

triple criteria of haemodialysis treatment for > 90 days, BMI >35 kg/m^2, and potentially suitable for kidney transplantation following weight loss.

The candidate then conducted a more detailed search of the medical records of the patients identified during preliminary screening, to determine if patients met the full study criteria and were eligible to participate in the study (Table 10). The candidate is a Registered Dietitian with extensive clinical experience with patients with CKD, and obtained permission to access clinical records and talk to patients at NHS sites hosting the research study.

Table 10: Inclusion and exclusion criteria for patient participation in a prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in haemodialysis patients - pilot study

Inclusion criteria	Exclusion criteria
Male or female, aged > 18 years	Pregnancy
Previously attempted weight loss	History of chronic liver disease
Fit for anesthesia and surgery	Previous bariatric surgery, gastric surgery or large hiatus hernia
Body Mass Index > 35 kg/m^2	Psychiatric illness including anxiety, mood and untreated eating disorders
Written informed consent	Malnutrition (assessed by subjective global assessment)
On haemodialysis for at least 90 days	Infection or course of antibiotics within the last month
	Current peritoneal dialysis treatment

Final Recruitment

Eligible patients were contacted initially by letter or approached in person in an outpatient clinic by the candidate or referred to the candidate by the patient's Nephrologist. All patients interested in accessing further information about the study were contacted by the candidate, either by telephone or in person, and were provided with verbal information and a written Information for Participants booklet on the study, with a follow up visit or telephone call 1-2 weeks later, where interested patients were given more information about the study protocol and an opportunity to ask questions about the study. Information provided to the patient at this stage focused on the choice of surgical or best medical care

treatment, anticipated risks and benefits of surgery and best medical care treatment, number of study visits required and further explanations of the tests involved. The candidate also emphasised that participation was voluntary and patients were free to withdraw from the study at any time without their medical care being affected.

Eligible patients wishing to be considered for surgical treatment were discussed with each patient's named nephrologist, and agreement that surgical treatment may be suitable was obtained prior to pre-surgery assessment. Patients wishing to undergo LSG weight loss surgery were referred to the study surgeon for assessment for LSG. A member of the surgical team completed the assessment, and the dietitian (the candidate) conducted an additional dietary assessment for weight loss surgery (method detailed in Appendix D). Patients may have required additional cardiovascular and respiratory assessments, and further surgical review, prior to being assessed as fit or unfit for weight loss surgery. Patients agreeing to participate in the study in the best medical care arm moved directly to the consent stage. Patients unsure whether they wished to participate were given more time to consider the study and the candidate contacted the patient again after a mutually agreed timeframe.

Consent

The process and meaning of informed consent was discussed, including the right of withdrawal at any time without compromising medical care. It was the responsibility of the person obtaining informed consent to assess capacity, and to ensure that they were satisfied that the patient understood the contents of the written Information for Participants booklet, the treatment choice offered, and the right to withdraw from the study at any time without penalty. If the patient was willing to participate in the study, either the candidate, or the study surgeon or the patient's named nephrologist obtained written informed

consent. One copy of the completed consent form (Appendix C) was given to the patient, one copy was filed in the medical notes and the original consent form was filed in the study master file, together with a copy of the Information for Participants booklet. All members of the study team had undertaken formal consent training and were able to assess capacity to consent.

Interventions

Patients were offered the choice of undergoing weight loss surgery using the laparoscopic sleeve gastrectomy procedure (LSG group) or continuing with best medical care (UC group).

Usual Care (UC)

All patients continued to receive medical treatment equivalent to that provided prior to study enrolment, including use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, erythropoiesis stimulating agents, iron, vitamin D, and phosphate binders; as well as therapies used to manage diabetes, obesity, other causes of CKD and other co-morbidities.

All patients were offered appropriate individualised dietary education and support for weight loss. Patients were invited to participate in existing weight loss programmes and/or exercise on dialysis schemes, attend supervised physical activity sessions or perform a home exercise programme. In this study, active intervention for weight loss was optional in the UC treatment arm to reflect true usual care, and patients who participated in this arm of the study did not nessessarily choose to participate in a weight loss intervention.

Laparoscopic Sleeve Gastrectomy Weight Loss Surgery (LSG)

Patients who elected to have weight loss surgery received best medical care, and some patients underwent laparoscopic sleeve gastrectomy, prior to the study ceasing early. Sleeve gastrectomy as a primary procedure consisted of a subtotal gastric resection of the fundus and body, to form a tube like stomach along the lesser curvature, with a final volume of 100 – 200 ml (Iannelli, Dainese et al. 2008). The surgery was performed by an experienced minimal access surgeon, Mr Ameet Patel, who had already performed at least 50 sleeve gastrectomy procedures. Resected tissue samples were examined for evidence of helicobacter pylori, and treatment with a proton pump inhibitor and antibiotics was commenced if positive.

Post Surgery Dietary Intervention

Patients were provided with dietary education and renal-specific written information prior to the procedure or 1-2 days post the procedure as an inpatient. Dietary intake and adequacy was reviewed at 1, 4, 6 and 12 weeks post-sleeve gastrectomy, then at 3-monthly intervals, and further education and written information was provided as required, until the study was terminated. Dietary intake progressed in texture from liquid to puree, then to soft foods over 3 months, before finally re-introducing most normal foods 4 - 6 months post surgery (Snyder-Marlow, Taylor et al. 2010). Volume of food or fluid intake was limited to 100 - 150 ml per meal, up to 6 times a day. This level of intake is sustainable due to the reduced stomach volume. Intakes greater than 150 ml may stress the suture line and create a leak, or may stretch the surgically reduced stomach capacity, increasing the risk of compromising the physical restriction imposed by the surgery, which may impede weight loss.

Dietary energy intake was restricted to approximately 1000 kcal per day post sleeve gastrectomy. Protein intake was optimised for haemodialysis at 1.2 g protein/kg ideal body weight (IBW)/day (EDTNA/ERCA Dietitians' Special Interest Group 2002), and additional protein was provided via nutritional supplements (Prosource Liquid: Nutrinovo, UK; Fortisip Extra/Fortimel: Nutricia Clinical, UK) if required. The remaining dietary energy was consumed from carbohydrate and fat sources, with low fat choices strongly encouraged. Patients were also recommended to enjoy a wide variety of tolerated foods. All patients were encouraged to modify sodium intake to a "no added salt" diet level, of 80 - 100 mmol sodium per day (EDTNA/ERCA Dietitians' Special Interest Group 2002). Potassium and phosphate intake was adjusted depending on residual kidney function, to maintain serum biochemistry within the recommended ranges (Abbott, Glanton et al. 2004; Renal Association 2007). A daily multivitamin and mineral supplement suitable for patients with CKD was prescribed.

Measurements

A brief description of all measures is included here. An in-depth description of those measures requiring a specific method of measurement or technique is outlined in Appendix D. All measures were performed at the start of the study and then at 3-monthly intervals until the study was terminated.

Demographics

Baseline demographic data including date of birth, ethnicity, gender, and cause of CKD (if known) were recorded at study enrolment. History of diabetes, cardiovascular disease, hypertension, dyslipidaemia, and surgical history were recorded at baseline. Medication use, including daily or weekly doses, was recorded at each study visit.

Laboratory assessments

Venous blood samples were collected in blood collection tubes (BD Vacutainer BD: New Jersey), immediately prior to the start of dialysis, after a 12-hour fast, at baseline and at 3-monthly intervals until the study was terminated. Multiple samples were collected in EDTA coated tubes (2 x 8 mL, 2 x 4 mL) for PBMC collection for endothelial progenitor cell counting with FACS analysis and cell culture of CFU-Hill colony forming units, full blood count, and plasma extraction, fluoride and oxalate containing tubes (1 x 4 mL) for serum glucose, and silica coated serum separating tubes (3 x 5 mL) for serum leptin, adiponectin, fetuin-A, IL-6, lipids, hs-CRP, and insulin.

Cell culture and flow cytometry

Samples for PBMC extraction were processed within 2 hours of collection, and a detailed description of the methods for preparation of PBMC cell culture is presented in Appendix D. PBMC were extracted using Ficoll-Paque PLUS (StemCell Technologies: France) density gradient centrifugation. The layer of mononuclear cells was collected, and washed twice with PBS with 2% foetal FBS Gold bovine serum (PAA: Austria). One quarter of the sample was suspended in 1 ml of CryoMaxx freezing medium (PAA: Austria) and the viable cells were counted using a Neubauer haemocytometer. The sample was frozen slowly and stored at -80°C, for later analysis of endothelial progenitor cells using fluorescence-activated cell sorting (FACS) flow cytometry.

A 5-day cell culture was performed with the remainder of the PBMC sample to develop "colony forming units" (Hill, Zalos et al. 2003), known as CFU-Hill colonies. The PBMC were plated, in duplicate, on fibronectin-coated 6-well plates in CFU-Hill liquid medium (StemCell Technologies: France), and incubated for 2 days to remove mature endothelial

cells and some monocytes. After 2 days the non-adherent cells were removed, counted, and re-plated, in duplicate, on fibronectin-coated 24-well plates in fresh medium and returned to the incubator. After 3 days, the non-adherent cells were removed, the wells washed and the culture fixed with methanol and stained with Giemsa staining solution (Merck: Germany). The CFU-Hill colonies were identified as a cluster with a central core of round cells with elongated spindle shaped cells radiating at the periphery, and were counted using a standard light microscope.

In preparation for endothelial progenitor cell counting with flow cytometry, frozen PBMC were rapidly thawed in a 37°C water bath then washed twice in culture medium (RPMI with 10% foetal bovine serum and 1% penicillin and streptomycin), by centrifugation at 300g for 8 minutes at 24°C with the brake ON. The cells were re-suspended in medium and viable cells counted, and washed again in PBS with 2.5% foetal bovine serum.

Cells were incubated with immunofluorescent-labelled antibodies against CD34+, KDR+ and CD133+ and corresponding isotype controls for 30 minutes at 4°C, washed twice, fixed in paraformaldehyde and suspended in PBS. Quantitative analysis of cells expressing CD34+, KDR+ and CD133+ and co-expressing CD34+/KDR+ and CD133+/KDR+ and CD133+/CD34+ /KDR+ was performed on the prepared cells and control samples using FACS analysis (BD FACS-Canto II: Belgium).

Biochemistry

The remaining sample for plasma was centifuged upon arrival in the laboratory and all serum samples were left for 30 minutes to clot before being spun. Samples for glucose, high density lipoprotein (HDL) fraction and total cholesterol, and a full blood count were processed immediately and the remaining serum and plasma was stored in aliquots at -80°C

for later analysis of serum leptin, fetuin-A, adiponectin, hs-CRP, IL-6 and insulin. Serum and plasma were stored in case further biomarkers were added to the study at a later date. Commercially available quantitative sandwich enzyme-linked immunosorbent assays were used to measure serum leptin and adiponectin (R&D Systems: USA), fetuin-A (Assay Pro: USA), IL-6 (Randox: United Kingdom) and insulin (Siemens: United Kingdom). Standard enzymatic techniques were used to measure the hs-CRP (Cormay: Poland), glucose (Siemens: United Kingdom), HDL fraction (Siemens: United Kingdom) and total cholesterol (Siemens: United Kingdom) on an Advia 2400 Chemistry System (Siemens: United Kingdom). HOMA-IR was used to calculate an index of insulin resistance from the product of the fasting concentrations of serum insulin (microunits/ml) and serum glucose (mmol/l) divided by 22.5 (Matthews, Hosker et al. 1985). The full blood count was performed using standard laboratory methods.

Nutrition assessment

Adherence to dietary guidelines was assessed with 3-day food intake records plus dietary interview to clarify and substantiate the content at baseline and every 3 months. Nutritional status was measured with Subjective Global Assessment (Detsky, MacLaughlin et al. 1987).

Anthropometry

Height was measured to the nearest 1cm without shoes using a wall mounted stadiometer. Weight was measured to the nearest 0.1 kg on a calibrated electronic scale with the patient wearing light clothing and without shoes. Waist and hip circumferences were measured to the nearest 0.1 cm at the level of the umbilicus and the widest point around the buttocks, respectively, with a calibrated plastic tape measure.

Other measures

Arterial stiffness was measured by brachial-femoral pulse wave velocity (PWV). PWV was measured with the patient lying supine, on an inter-dialysis day (Di Iorio, Nazzaro et al. 2010) using the Vicorder device (Skidmore Medical, United Kingdom), with cuffs placed around the upper thigh and the upper arm (brachial-femoral). The distance from the top of the brachial cuff to the top of the femoral cuff, in a straight line, was measured with a calibrated plastic tape measure, and entered into the Vicorder software, and PWV was calculated from this distance and the pulse transit time between the 2 points. The measurement was performed twice and the average of the 2 measures used. Inter- and intra- tester reliability was measured prior to the study.

BP was measured with the patient seated in the dialysis chair, using an appropriate-sized cuff on the non vascular access arm prior to dialysis. To account for changes in BP with changes in body water, mean monthly pre-dialysis blood pressure was calculated from thrice weekly pre-dialysis blood pressures recorded in dialysis patient records.

Quality of life was assessed using the self-adminstered short form 36 (SF-36) questionnaire (Appendix B) and the self-administed Hospital Anxiety and Depression Scale (HADS) (Appendix B) (Zigmond and Snaith 1983; Lacson, Xu et al. 2010).

Predefined complications of weight loss surgery included poor tolerance of liquids/puree/ soft diet, gastrectomy leak, bleeding requiring transfusion, bleeding or restriction requiring surgical or endoscopic intervention, longer than expected hospital admission, readmission to hospital directly related to weight loss surgery, post-operative infection, and 30 day mortality; and were recorded as soon as they became known to the study team. The event

rate of post-operative complications was compared to the pooled event rate from published studies.

Adverse events, including compromised dialysis access, cardiovascular events including myocardial infarction, stroke and hospitalisation for heart failure, gastro-oesophageal reflux, heart rhythm irregularities, malnutrition, dehydration, vomiting, hypoglycaemia, diarrhoea, constipation, epigastric pain, oedema and hospitalisation during the study period, were reported and recorded at study visits.

Statistical Analysis

Sample size calculation

In a population with a mean BMI of 42.0 kg/m^2 and standard deviation of 5.9 kg/m^2 at baseline, with the assumption that 70% of the surgery group and 10% of the usual care group will reach the BMI cut-off of <35 kg/m^2 after 12 months, with type 1 error set at 5% and 80% power, 12 patients were required in each group. The planned study sample size was 15 patients in each group, to allow for drop-outs.

Data analysis

Due to the exploratory nature of this pilot study, the statistical analysis plan was limited to tests suitable for small samples. Statistical analysis was performed using IBM SPSS Statistics 19.0 software. Descriptive statistics are expressed as median (± IQR) values for continuous outcome variables and percentage values for categorical variables. Differences between groups were analysed with the Hodges-Lehman median difference test for continuous variables and Pearson's Chi Squared test or Fisher's exact test for categorical variables. It was planned to observe trends in the data over time and determine effect sizes

with weight loss within and between treatment groups with mixed modelling, with time as a random factor, however this was not possible with the amount of data collected.

It was intended to compare the number of patients meeting the BMI cut-off criteria for transplant, and adverse event rate between treatment groups with Fisher's exact tests. Complication rates in the haemodialysis LSG group were to be compared to the event rate in published studies of the general population, using contingency tables and Fisher's exact test. However, due to the small number of patients included in the study at termination, these comparisions would not be valid. Instead, the primary event rates are reported but no statistical comparisions have been made.

Relationships between weight loss and changes in exploratory outcomes, BP, quality of life, insulin resistance and blood lipids were to be investigated with simple linear regression analyses. These analyses were not possible with the amount of data collected prior to the early termination of the study.

Study withdrawals and reasons for withdrawal were collected and analysed descriptively.

Results

Adverse events, study governance and early cessation of study

The culmination of several events related to this study resulted in the suspension of the study half way through the planned study period. A timeline of pertinent study events and milestones from inception to early termination and the post termination period is presented in Figure 10.

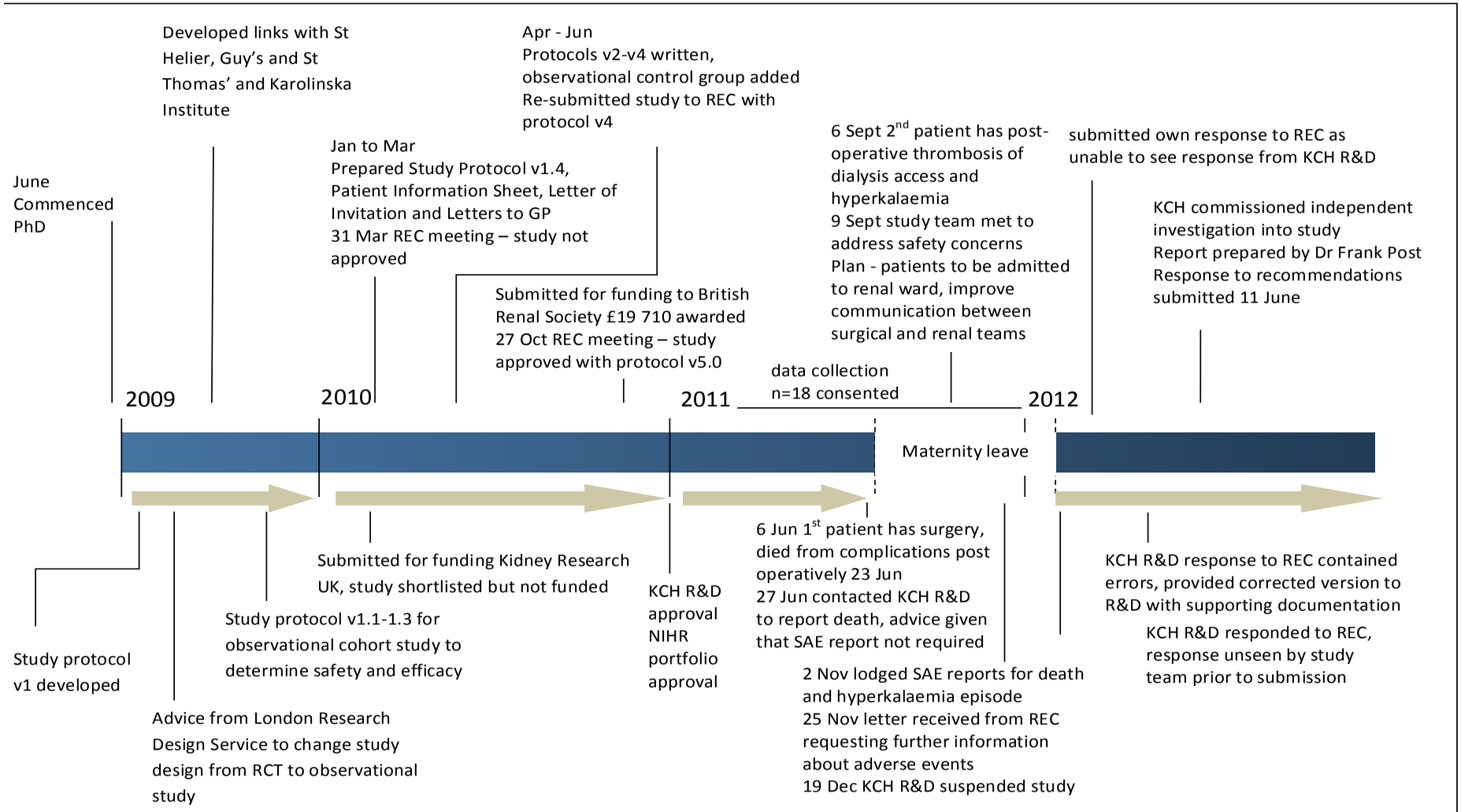


Figure 10: Timeline of events in "A Prospective Cohort Study of Laparoscopic Sleeve Gastrectomy for Obese Patients on Haemodialysis: pilot study"
GP, General Practitioner; KCH, King's College Hospital; NIHR, National Institute for Health Research; R&D, Research and Development Department

2 serious adverse events occurred between June and September 2011, and a combination of proceedings led to the late reporting of these events to the Research Ethics Committee. Following submission of the reports in November 2011, the Research Ethics Committee issued a notice to suspend the study pending a request for further information relating to the 2 events and study governance in December 2011. Before this information could be provided to the ethics committee, the King's College Hospital Research and Development Department terminated the study site approval, and submitted a response to the Research Ethics Committee. The response contained factual errors and the study team was asked to provide a corrected version, substantiated with documented evidence, to the King's College Hospital Research and Development Director. An independent mediator was recruited to review the study, including all documentation and reports, and make recommendations.

The study results obtained prior to suspension and early termination of the study are presented below. Body weight data and transplantation listing status was obtained from clinical records and included up to 12 months, with permission from the Research and Development Directorate.

Characteristics of study participants

Patients undergoing haemodialysis at the study sites were screened for possible inclusion in the study, and a flow diagram of patient recruitment is displayed in Figure 12. At the point when the study was terminated, 51 patients met the screening criteria of BMI > 35 kg/m^2 and aged > 18 years and were approached to participate in the study. 19 patients were excluded for the following reasons: they were unlikely to qualify for kidney transplantation regardless of BMI (n = 5); BMI had decreased below 35 kg/m^2 (n = 2); they were absent from their dialysis unit during the entire recruiting period (n = 1); or they declined to participate (n = 11). Of the remaining 32 patients, 8 patients were already assessed and on

the waiting list for laparoscopic sleeve gastrectomy, 12 patients expressed an interest in weight loss surgery and were given an appointment with the study surgeon and 12 patients were considering participating as observational controls.

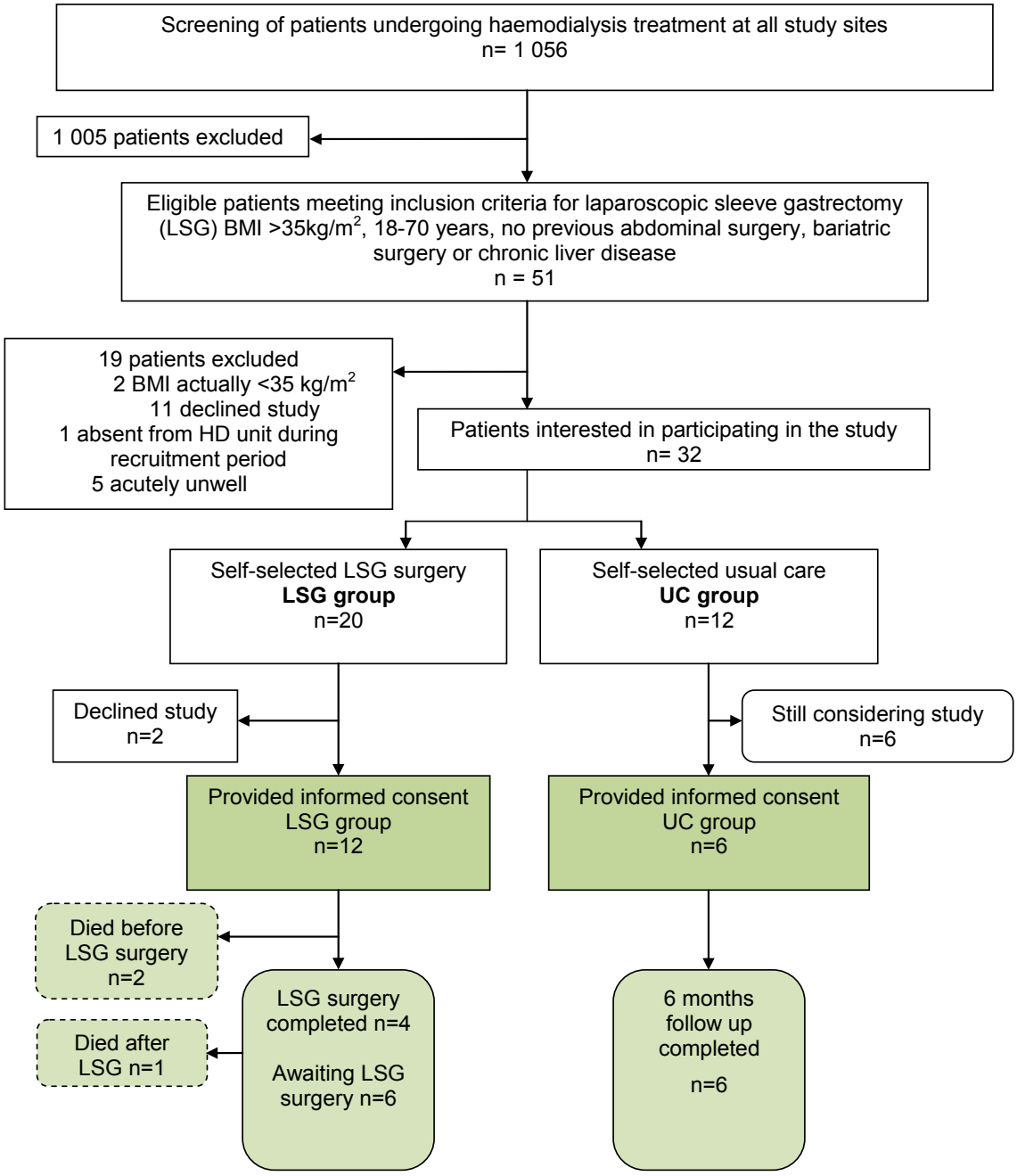


Figure 12: Flow chart showing patient recruitment to a prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in obese patients on haemodialysis - pilot study

Prior to study suspension in December 2011, 18 patients had consented to participate in the study. 12 patients had commenced the study, 6 in the sleeve gastrectomy (LSG) group

(all approved for sleeve gastrectomy surgery prior to being approached for the study) and 6 gender- and age-matched, patients in the best medical care (UC) group. A further 6 patients were recruited to the LSG group, but had not yet commenced the study, including 2 patients who died after providing informed consent, but prior to the baseline assessment. The characteristics of the patients who consented to the study are presented in Table 11. The group of patients who had consented but not yet commenced the study had similar characteristics to the patients electing LSG who did commence the study, except that there was a greater prevalence of diabetes in those who did not commence the study. The causes of death in the 2 patients who died prior to commencing the study were acute coronary syndrome, and hospital acquired pneumonia during admission for aortic valve replacement.

Table 11: Baseline characteristics (median ± IQR; or %) of obese patients on haemodialysis commencing a pilot study of laparoscopic sleeve gastrectomy for weight loss

Parameters	LSG group (n=6)	LSG group Consented but did not commence study (n=6)	UC group (n=6)	p
Age (years)	50.5 (44.8 to 60.8)	50 (47.5 to 58.5)	58 (55.5 to 64.3)	0.1
Gender (Female)	4 (67%)	3 (50%)	5 (83%)	0.2
Race (White/Black/Other)	3/2/1	5/1/0	3/3/0	0.2
Weight (kg)	113.3 (103.9 to 126.8)	113.5 (100.3 to 120.0)	105.5 (102.0 to 113.5)	0.5
BMI (kg/m²)	42.0 (38.5 to 45.2)	41.9 (38.5 to 42.7)	42.3 (36.9 to 43.4)	1.00
Diabetes	2 (33%)	4 (67%)	5 (83%)	0.01
Hypertension	6 (100%)	6 (100%)	4 (67%)	0.1
Sleep apnoea	2 (33%)	2 (33%)	1 (17%)	0.4
Metabolic Syndrome	6 (100%)	5 (83%)	6 (100%)	0.3

BMI, body mass index; IQR, inter-quartile range; LSG, laparoscopic sleeve gastrectomy; UC, best medical care

At baseline, all patients met the revised ATP III criteria for metabolic syndrome, with at least 3 of the 5 risk factors present: increased waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated BP or on antihypertensive treatment, and elevated fasting glucose or on drug treatment for elevated glucose (Grundy, Cleeman et al. 2005). There were more females, and more patients with diabetes, in the UC group. Median BMI for all patients was 42.3 kg/m², and BMI was well matched between groups. The primary cause of kidney disease was diabetes or hypertension in

7 patients, primary glomerulonephritis in 2 patients, adult polycystic kidney disease in 1 patient; in 2 patients the cause of kidney disease was not known.

In the LSG group who had surgery or had a planned date for surgery (n = 6), the mean (±SD) length of time from obtaining consent to the date of surgery (or planned surgery date) was 6.5 months (±3 months). The overall waiting time for surgery in this group was 11.3 months (±2 months), as 5 of the 6 patients were already waitlisted for surgery before the study commenced.

4 patients underwent LSG surgery to reduce stomach size by 2/3 to induce weight loss by restricting food intake. Median inpatient length of stay was 11 days (range 6 - 17 days) and helicobacter pylori infection was negative in all cases. The other 2 patients had both been allocated admission dates for surgery prior to study termination, but both admissions were cancelled due to lack of availability of hospital beds on the dates of planned admission.

In the UC group, patients were offered support for weight loss, and were able to choose their own level of weight loss intervention, to best reflect true usual care for obese patients on haemodialysis in the study centres. 3 patients elected to join the renal Weight Management Programme, attending a multidisciplinary clinic once a month for 6 months, following a low fat diet, increasing physical activity and were prescribed orlistat 120mg tds, with self monitoring and patient led goal setting to facilitate behaviour changes (refer to Chapter 5 for full details of the Weight Management Programme). 1 patient elected to make dietary and physical activity changes independently, and 2 patients maintained their current lifestyle and made minimal changes to their diet or physical activity.

Achievement of BMI criteria for kidney transplantation waitlisting

The study was ceased prior to any patients in the LSG group reaching 6 months follow up, with only standard clinical care follow-up permitted once the study was ceased, thus only body weight data are available up to 12 months. All 6 patients in the UC group had 6 months follow up in the

study, at the time the study was terminated. Data on changes in body weight, BMI and achievement of transplantation listing criteria of BMI < 35 kg/m² are presented in Table 12. In patients undergoing LSG, median BMI decreased by 15.5%, to 33.5 kg/m², after 3

Table 12: Changes in body weight, body mass index (BMI) and kidney transplantation waitlisting in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Patient and Group	Age (yr)	Sex	Weight (kg) (BMI)	Weight change (kg)			BMI change (kg/m²)			Kidney transplantation	
				3 mth	6 mth	12 mth	3 mth	6 mth	12 mth	BMI <35 kg/m²	Work up started
LSG 1	43	F	103.0 (40.2)	-15.5	-20.0	-24.0	-6.1	-7.9	-9.5	Yes	Yes
LSG 6	51	F	106.5 (43.8)	-25.0	-28.5	-35.0	-7.6	-11.7	-14.4	Yes	Yes
LSG 9	32	M	120.0 (35.8)	-18.0	-23.0	-22.0	-5.3	-9.5	-6.5	Yes	Yes
UC 1	67	M	97.0 (35.2)	0	0	-0.5	0	0	-0.2	No	No
UC 2	57	F	102.0 (35.3)	0	0	-1.0	0	0	-0.4	No	No
UC 3	55	F	123.0 (43.6)	0	0	0	0	0	0	No	No
UC 4	51	F	115.0 (42.8)	-1.0	-2.0	-5.0	-0.6	-0.8	-1.9	No	No
UC 5	66	F	109.0 (44.2)	0	-9.0	-10.5	0	-3.6	-4.2	No	No
UC 6	59	F	102.0 (41.9)	-3.0	-8.0	-10.0	-1.2	-3.3	-4.1	No	No

BMI, body mass index in kg/m²; F, female; LSG, laparoscopic sleeve gastrectomy; M, male; mth, months post intervention; UC, usual care.

months, and decreased by 2.6% to 41.2 kg/m² in the UC group over the same time period. After 6 months, median BMI decreased by 23.7%, to 31.1 kg/m² in the LSG group, and by 6.5%, to 39.6 kg/m² in the UC group. At 12 months medium BMI had decreased by 30% in the LSG group, to 29.4 kg/m², and by 8.2% in the UC group, to 38.9 kg/m². Statistical analyses were not performed, however, it is reasonable to state that the weight loss achieved after LSG is, at least clinically, significantly greater than the weight loss achieved after UC. All patients in the LSG group were listed for kidney transplantation within 6 months of weight loss surgery, compared to none of the patients in the UC group, over the same time period. One patient (LSG9) has since received a kidney transplantation from a living donor.

Safety of sleeve gastrectomy in haemodialysis

There were no adverse events in the UC group. Two serious adverse events had occurred in the LSG group at the time of study termination.

In one patient (LSG 2), a small vessel was perforated to a length of 1mm during surgery, and required repair by laparotomy, post operatively. The bleed was not able to be stopped quickly and respiratory and cardiac arrests followed. The patient unfortunately remained comatose and died 17 days later.

The second adverse event related to post-operative failure of the patency of the patient's (LSG 9) femoral polytetrafluoroethylene (PTFE) graft used for vascular access in haemodialysis, together with post-operative hyperkalaemia. Patients usually have femoral dialysis access sites created when all sites for upper limb access have been exhausted. A haemodialysis arterio-venous fistula (created with native vessels) or graft (created with an artificial component and native vessels) is formed to enable access to a large vessel to allow blood to flow out of the patient's body, through the haemodialysis filter and back into the patient's bloodstream. These permanent forms of dialysis access have a lower risk of infection than that associated with temporary venous catheters for haemodialysis access, often used for emergency access. After LSG surgery, the patient developed combined respiratory and metabolic acidosis, and a rise in serum potassium, requiring urgent haemodialysis and airway support. The patient's existing graft lost patency and could no longer be used to provide haemodialysis. The patient was then admitted to the Surgical Critical Care Unit with on-going hyperkalaemia. The potassium level continued to rise and several attempts were made prior to successful insertion of a temporary femoral catheter, with radiological guidance, after which haemofiltration was provided and the serum potassium level returned to normal. The blocked fistula required thrombectomy and fistuloplasty to return it to patency.

Co-morbidities and quality of life

All collected data on BP, insulin resistance and total cholesterol to HDL ratio are presented in Table 13.

Median BP was 151/76 mm Hg in the UC group and 151/77 mm Hg in the LSG group at baseline. Systolic BP increased slightly after 3 months, with median BP 154/65 mm Hg, and then decreased at 6 months to a median of 123/68 mm Hg in the UC group. Diastolic BP was generally well controlled in the UC group across the 6-month observation period. The rise in BP at 3 months may be attributable to the temporal development of fluid overload in the patient UC 5, as the dry weight was not reduced temporally with the intentional weight loss. Once the dry weight was corrected, the patient's BP decreased accordingly. BP lowering medications were not changed in 5 of the 6 patients in the UC group, and an additional antihypertensive agent was added for 1 patient.

Table 13: Blood pressure, insulin resistance and blood lipids in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Measure		Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)			HOMA-IR			Total cholesterol to HDL ratio		
	Month	0	3	6	0	3	6	0	3	6	0	3	6
LSG	LSG 1	158			80			4.3			3.3	2.6	
group	LSG 2*	143			60			11.1			5.0		
	LSG 6	141			74			1.9			3.6		
	LSG 9	163			90			3.9			3.0		
UC	UC 1	156	124	122	82	68	65	3.4	3.7	4.4	4.0	4.3	3.8
group	UC 2*	166	176	165	77	79	89	9.8	2.5	2.6	3.4	3.5	3.6
	UC 3*	148	173	123	82	90	67	10.2		30.2	4.8	4.8	3.9
	UC 4*	101	102	104	60	60	62	85.0	52.7	57.4	5.9	5.6	6.0
	UC 5*	153	171	140	74	62	79	27.8	15.8		4.5	5.0	4.4
	UC 6*	133	136	119	72	57	69	4.7	9.0		3.1	2.6	2.6

* patient has diabetes and uses insulin; HDL, high density lipoprotein; HOMA-IR. homeostasis method of assessment – insulin resistance; LSG, laparoscopic sleeve gastrectomy; UC, usual care

HOMA-IR was higher in patients with diabetes than in those without diabetes. HOMA-IR is associated with body weight (Spearman r = 0.67, p = 0.04), waist circumference (Spearman r = 0.62, p = 0.05) and triglycerides (Spearman r = 0.74, r = 0.01) in all patients at baseline. However HOMA-IR was only associated with adiponectin in patients without diabetes at baseline (Spearman r = 1.00, p < 0.001). There was no association between HOMA-IR and endothelial progenitor cell function (CFU-Hill colony counts) or arterial stiffness (brachial to femoral PWV) in patients with, or without diabetes, at baseline.

Median total cholesterol to HDL cholesterol ratio was 4.3 in the UC group and 3.6 in the LSG group at baseline. The ratio remained at 4.3 after 3 months and was 3.9 after 6 months in the UC group.

Table 14 lists the individual changes in the self-administered quality of life measures chosen for this study; the HADS scores (Zigmond and Snaith 1983) and the SF-36 Health Survey (Ware, Snow et al. 2000).

Table 14: Quality of life scores in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Measure		Anxiety Score HADS			Depression Score HADS			SF-36 physical domain			SF-36 mental domain		
	Month	0	3	6	0	3	6	0	3	6	0	3	6
LSG group	LSG 1	4			4			36.4			41.2		
	LSG 2	7			3			44.3			35.3		
	LSG 6	11			9			28.9			42.5		
	LSG 9	12			9			30.3			36.0		
UC group	UC 1	1	4	2	2	6	2	38.4	39.0	35.4	45.2	52.1	45.3
	UC 2	1	0	1	1	2	1	32.0	25.9	29.0	39.7	40.6	48.2
	UC 3	9	10	9	8	7	9	21.1	34.5	20.4	50.5	31.2	44.8
	UC 4	8	6	1	2	1	1	24.8	27.2	34.9	53.0	45.5	32.7
	UC 5	1	0	1	1	1	1	46.1	33.9	43.2	57.0	64.0	64.0
	UC 6	1	1	1	1	1	1						

HADS, Hospital Anxiety and Depression Scale; LSG, laparoscopic sleeve gastrectomy; SF-36, Short Form (36) Health Survey; UC, usual care

Median SF-36 scores for the whole study population were 32.0 for the physical domain and 42.5 for the mental domain. Both the HADS and the SF-36 quality of life measures indicated a trend towards poorer mental health scores in the LSG group than in the UC group at baseline. Anxiety and depression scores were higher (worse) at baseline for the LSG group than for the UC group, although not statistically significantly different. Median SF-36 mental health domain scores were significantly lower in the LSG group, compared to the UC group, at baseline (UC 50.5, LSG 38.6; p = 0.048). Anxiety and depression scores were largely unchanged over time in the UC group. After 3 and 6 months, UC group mental health domain scores decreased by 5.0, and 5.2, respectively, although this is not thought to represent a clinical difference in mental health over time. Median SF-36 physical domain scores were 32.0 in the UC group and 33.4 in the LSG group at baseline (p = 1.00). In the UC group, the median physical domain score remained quite steady, increasing by 1.9 after 3 months and 2.9 after 6 months.

Exploratory outcomes

Additional exploratory measures of anthropometry, arterial stiffness and endothelial progenitor cell function (CFU-Hill colony counts) (Table 15) and markers of inflammation

Table 15: Anthropometry, vascular stiffness and Hill-Colony Forming Units (CFU-Hill) in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Measure		CFU-Hill colony count per 10^{6} MNC			Brachial to femoral PWV (m/s)			Waist circumference (cm)			Waist to Hip ratio		
	Month	0	3	6	0	3	6	0	3	6	0	3	6
LSG	LSG 1	0			16.2			125.5			0.98		
group	LSG 2	11.8			10.8			146.6			1.03		
	LSG 6	3.3			10.4			117.1			0.89		
	LSG 9	3			34.2			127.6			1.02		
UC	UC 1	4.5	4.3	4.5	16.8	17.6	26.7	124.3	123.8	123.7	1.08	1.05	1.04
group	UC 2	0	0	0	14.1	14.4	13.6	132.5	130.7	133.6	1.05	1.01	1.04
	UC 3	10		4.8	13.4	13.0	19.7	136.5	138.8	138.7	0.99	1.02	1.08
	UC 4	2.3	2.1	0.8	13.4	19.3	16.0	141.7	139.2	141.0	1.12	1.14	1.15
	UC 5	0.5	0.5		36.4	40.3		122.3	127.5	125.5	0.91	0.94	0.94
	UC 6	2.3	2.5		4.4	3.7		126.8	126.6	124.0	0.93	0.95	0.94

LSG, laparoscopic sleeve gastrectomy; m/s, metres per second; MNC, mononuclear cells; PWV, pulse wave velocity; UC, usual care

(Table 16), and adipokines and fetuin-A (IL-6 was elevated in 3 of the 6 patients with elevated CRP, and there was no association between the inflammatory markers IL-6 and CRP at baseline (Spearman r = 0.37, p = 0.3). Six of the 10 patients had an elevated hs-CRP, defined as CRP > 5mg/L, at baseline. In the UC group, those with an elevated hs-CRP at baseline continued to have an elevated hs-

Table 17) were assessed every 3 months, until the study was suspended. Counts of CD133+, CD34+ and KDR+ cell by flow cytometry FACS analysis had not yet been performed when the study was terminated, as the samples were prepared and stored for later analysis.

Median brachial to femoral PWV was 13.5 m/s in the LSG group and 13.8 m/s in the UC group at baseline. PWV remained relatively stable over 6 months in the UC group. Median waist to hip ratio was 1.00 in the LSG group and 1.02 in the UC group at baseline, and did not change over the study in the UC group.

Figure 13 is a CFU-Hill colony at day 5 in culture from 1 of the study patients, after fixation with methanol and staining with Giemsa Blue. A colony is defined as a cluster of rounded cells surrounded by radiating spindle shaped cells. For each patient the mean of

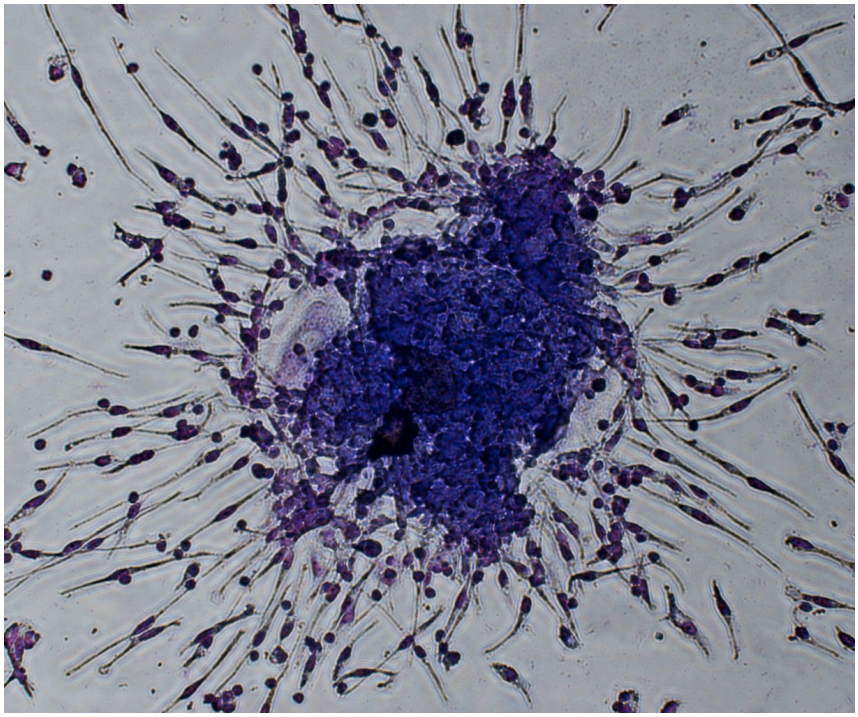


Figure 13: A CFU-Hill colony at day 5 in culture medium from a haemodialysis patient (x20 magnification)

all four CFU-Hill cell cultures prepared, was calculated at each time point. Average within-patient CFU-Hill colony counts ranged between 0 and 118 colonies per 10^7 cultured mononuclear cells at baseline, and the median colony count was 26.5 (IQR 5-45). In the UC group CFU-Hill counts were either stable or declined during the 6-month follow-up period. One patient in the UC group consistently produced no CFU-Hill colonies in any of the 3 cell cultures performed over 6 months.

Table 16: Markers of inflammation in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Measure		IL-6 (ng/L)			hs-CRP (mg/L)		
	Month	0	3	6	0	3	6
LSG	LSG 1	3.8			1.7		
group	LSG 2	2.0			10.1		
	LSG 6	28.5			38.3		
	LSG 9	2.6			11.9		
UC	UC 1	7.2	7.2	167.6	9.5	22.4	11.3
group	UC 2	3.8	3.7	0.4	1.1	2.5	6.1
	UC 3	20.0		12.4	13.7		22.5
	UC 4	13.4	16.7	15.8	16.3	48.1	31.8
	UC 5	2.6	2.8		1.9		
	UC 6	3.1	2.9		2.8	3.9	

hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin 6; LSG, laparoscopic sleeve gastrectomy; UC, usual care

IL-6 was elevated in 3 of the 6 patients with elevated CRP, and there was no association between the inflammatory markers IL-6 and CRP at baseline (Spearman r = 0.37, p = 0.3). Six of the 10 patients had an elevated hs-CRP, defined as CRP > 5mg/L, at baseline. In the UC group, those with an elevated hs-CRP at baseline continued to have an elevated hs-

Table 17: Adipokines and Fetuin-A in obese patients on haemodialysis undergoing laparoscopic sleeve gastrectomy for weight loss

Measure		Fetuin-A (mg/L)			Adiponectin (mg/L)			Leptin (µg/L)		
	Month	0	3	6	0	3	6	0	3	6
LSG	LSG 1	747.0			22.1			719.3		
group	LSG 2	481.2			10.5			388.8		
	LSG 6	393.7			14.4			56.5		
	LSG 9	601.5			6.4			238.8		
UC	UC 1	790.9	476.3	1874	21.4	10.2	16.6	95.2	60.1	32.2
group	UC 2	402.5	564.7	468.2	24.0	26.6	24.9	87.3	119.8	58.6
	UC 3	643.2		501.5	10.8		9.3	427.5		79.2
	UC 4	606.8	710.6	527.0	21.4	15.6	20.9	198.9	204.5	262.1
	UC 5	626.7	438.3		12.0	17.9		303.0	136.0	
	UC 6	482.4	497.4		22.9	34.6		269.3	204.9	

LSG, laparoscopic sleeve gastrectomy; UC, usual care

CRP at 6 months. Median (IQR) for fetuin-A at baseline was 604 (481-643) mg/L, and there was no relationship between fetuin-A and either adiponectin, HOMA-IR, arterial stiffness, systolic blood pressure, body weight, waist circumference, HDL cholesterol or triglycerides at baseline in the study sample.

Total adiponectin was inversely correlated with baseline body weight (Spearman r = -0.82, p = 0.04), and did not differ between groups at baseline. Serum leptin levels varied widely in the sample population, and ranged from 56.5 to 717.3 µg/L. Median leptin was 313.8 µg/L in the LSG group and 234.1 µg/L in the UC group at baseline. Leptin levels decreased over 6 months to 68.8 µg/L in the UC group. Baseline leptin was not associated with body weight (Spearman r = 0.44, p = 0.2) or BMI (Spearman r = 0.33, p = 0.3) at baseline.

Discussion

This pilot study was designed to study the efficacy and safety of the LSG for weight loss in obese patients with kidney failure undergoing haemodialysis. As the King's College Hospital Research and Development Directorship stopped the study early, due to the occurrence of 2 serious adverse events, the study was unable to achieve its aim. The results are inconclusive. The following discussion will largely focus on determining the risks of LSG in obese haemodialysis patients and the ethical considerations in early cessation of research in clinical studies.

Effect of weight loss surgery on kidney transplantation waitlisting

All 3 surviving patients who underwent LSG, but no control patients, lost sufficient weight to reduce their BMI to < 35 kg/m^2 and have commenced the process of assessment and preparation for kidney transplantation waitlisting or kidney transplantation from a living donor. This is consistent with our previous uncontrolled observational study of obese patients with CKD undergoing LSG surgery, in which 4 out of 5 patients were listed for kidney transplantation after sufficient weight loss was achieved (MacLaughlin, Hall et al. 2012).

There are no other published studies of LSG in obese patients with CKD, however, gastric bypass and gastric banding have also been successfully used to achieve weight loss prior to kidney transplantation or waitlisting, with no peri-operative mortality reported (Newcombe, Blanch et al. 2005; Alexander and Goodman 2007; Koshy, Coombes et al. 2008; Takata, Campos et al. 2008; Modanlou, Muthyala et al. 2009).

Quality of Life

Baseline SF-36 scores in this study were similar to those reported in a study of 394 patients with stage 5 CKD and undergoing dialysis treatment in a Swedish CKD population (SF-36 physical domain 32.9; SF-36 mental domain 38.5), and both the study group as a whole and HD patients in the Swedish study had lower SF-36 scores than the Swedish population mean (SF-36 physical domain 50; SF-36 mental domain 50) (Pagels, Soderkvist et al. 2012), although the UC group had a similar score to the population mean for the mental health domain. The lower quality of life scores in the LSG group at baseline in the present study may go some way to suggest why those patients chose to undergo LSG, and those with higher quality of life scores chose not to be considered for weight loss surgery, given that treatment allocation was self-selected. The study was unable to determine whether these quality of life scores improved after weight loss surgery due to early termination of follow up data collection.

Exploratory Outcomes

PWV values for patients in this study were higher than recently reported reference values for the healthy population, with normal median values ranging between 7-8 metres/second for 40-60 year olds (The Reference Values for Arterial Stiffness Collaboration 2010), and also higher than reported for normal weight haemodialysis patients (Georgianos, Sarafidis et al. 2011), which may have been expected as PWV also increases with obesity (Safar, Czernichow et al. 2006).

Brachial to femoral PWV is relatively quick and simple to measure and can be performed post dialysis, although ideally it should be performed on an inter-dialysis day (Di Iorio, Nazzaro et al. 2010). However, without the full study data, the usefulness of PWV measurement, and inflammatory and adipose tissue markers, to monitor the cardiovascular

effects of weight loss in haemodialysis patients in future studies, cannot be commented upon.

As far as could be ascertained, there is only one other study measuring endothelial progenitors cells using the CFU-Hill colony culture assay in patients undergoing haemodialysis (Krieter, Fischer et al. 2010), and the results of the present study concur with the median CFU-Hill colony count of between 5.0 and 35.0 colonies per 10^7 mononuclear cells (range 0 - 262.5 per 10^7 mononuclear cells) for haemodialysis patients, (Krieter, Fischer et al. 2010), which is considerably lower that the intermediate level of 124 colonies per 10^7 mononuclear cells reported for healthy males (Hill, Zalos et al. 2003).

Analysis of CFU-Hill colony forming units is a time-consuming process that must be initiated immediately on fresh blood samples, and unless a 7-day laboratory support service is available, would not be practical in larger studies of haemodialysis patients. Without a 7-day cell culture service, samples for CFU-Hill cultures can only be collected on Wednesdays, so that Days 0, 2 and 5 fall on weekdays. However, this is not practicable, as only half of any haemodialysis population undergo dialysis on a Wednesday.

The techniques for quantitative analysis of cells expressing CD34+, KDR+ and CD133+ and co-expressing CD34+/KDR+ and CD133+/KDR+ and CD133+/CD34+/KDR+, including preparation and immunofluorescent-labelling of the extracted PBMC and control samples, using FACS analysis (BD FACS-Canto II: Belgium), were observed, learned and practised by the candidate, but not performed on the stored study samples prior to the early termination of the study.

Serum leptin was not directly associated with body weight in this small study sample, which supports the hypothesis that reduced kidney function results in a decrease in leptin clearance in CKD (Axelsson and Stenvinkel 2008), which is independent of leptin resistance resulting in hyperleptinaemia evident with obesity (Kelesidis, Kelesidis et al. 2010).

Adiponectin is associated with body weight in this study sample, and with HOMA-IR in patients without diabetes. Insulin resistance usually supresses adiponectin (Wiecek, Adamczak et al. 2007), but there was a direct correlation between adiponectin and HOMA-IR in this sample, and no evidence of an inverse relationship between leptin and adiponectin, indicating that adiponectin, and/or leptin may be increased in haemodialysis patients either due to a reduced GFR, or alternatively, adiponectin rises in response to a high level of inflammatory signalling (Rabin, Kamari et al. 2005) in an attempt to suppress the atherosclerotic processes (Ouchi, Kihara et al. 1999).

Levels of fetuin-A were similar to those published previously in haemodialysis patients (Hermans, Brandenburg et al. 2007). Fetuin-A is a strong inhibitor of vascular calcification, and is inversely related to arterial stiffness in non-diabetic patients with stages 3-4 CKD, and inversely with mortality in haemodialysis (Stenvinkel, Wang et al. 2005; Ford, Tomlinson et al. 2010). There was no inverse relationship between fetuin-A and adiponectin, as has been reported in earlier stages of CKD (Ix, Chertow et al. 2006), and also no relationship between fetuin-A and insulin resistance and other metabolic syndrome components, which was evident in obese children without CKD (Reinehr, Roth et al. 2008). These findings may suggest that in haemodialysis patients, the relationship between fetuin-A and obesity (or metabolic syndrome) may be overshadowed by the deranged metabolic state of vascular calcification. The effect of weight loss on fetuin-A levels in

obese haemodialysis patients cannot be elucidated from this study due to the early cessation of the research.

Safety and efficacy of weight loss surgery

This study attempted to monitor the safety and efficacy of LSG in obese patients with kidney failure undergoing haemodialysis. A series of events occurred, resulting in early termination of the study. The study was conducted following the study protocol, in which patients self-selected either LSG surgery, or maintained best medical care, and a range of clinical and laboratory based outcomes were measured at pre-established time points in all patients.

The first patient to undergo LSG in the study died following complications post surgery. This was discussed with the Research and Development Department at King's College Hospital, and as this patient was already due to undergo weight loss surgery prior to consenting to take part in the study, the event was deemed to be not directly related to the study. The Chief Investigator (the candidate) was informed at the time that the event did not need to be reported officially to the Research Ethics Committee.

Following the second case of LSG surgery, the haemodialysis team was not informed that this patient was being admitted and did not have adequate information to perform his haemodialysis safely without risking the patency of his vascular access graft. Problems developed when the access was used and then failed. This series of events was reported as a clinical adverse incident and it was unclear whether or not the access difficulties were directly related to the LSG surgery. At this point the candidate met with the study surgeon and the senior clinical investigator to discuss 2 issues; firstly, should the patients who have provided consent be informed about the 2 adverse events related to LSG in haemodialysis

patients, and secondly, how can communication between the medical and surgical teams be improved?

It was agreed that all patients with CKD undergoing LSG would be admitted to hospital under the care of the admitting Consultant Nephrologist on call, rather than the study surgeon. This would ensure that adequate communication between the teams occurred prior to admission and that all necessary arrangements for haemodialysis were in place. The medical and surgical opinion was that it was too early in the study to determine whether the risk of surgery was increased in these patients and that informing patients of the adverse events may create unjustified concern.

The 3rd and 4th sleeve gastrectomies proceeded uneventfully. Both the 5th and 6th procedures were cancelled due to the hospital being unable to allocate a bed for an elective surgical procedure on the days of the planned admissions. During completion of the study annual report in December 2011, the candidate informed the Research Ethics Committee of the 2 adverse events. The committee determined these events were related to the study, and requested both further information and a meeting with the Chief Investigator (the candidate), together with a representative from the Research and Development Department at King's College Hospital. Upon receiving copies of the event notifications and the response from the Research Ethics Committee, the Research and Development Department decided to suspend the study and investigate the events.

A meeting was held between the candidate, the lead clinical investigator and the Research and Development Manager, Director, and Deputy Director to discuss the events. The approval to conduct the study at the host site was withdrawn, as the Research and Development team deemed that the study had met the predetermined stopping criteria of

consistent observation of early or late post surgical complications. Additionally, the Research and Development team decided that the patients had not been informed sufficiently of the risk related to surgery and thereby could not provide informed consent.

The written report of the meeting sent to the Research Ethics Committee contained errors and inconsistencies. The candidate prepared and submitted a response, with documented evidence providing information to support corrections to the errors in the report. An independent investigation into the study and its governance was commissioned. Dr Frank Post, Senior Clinical Lecturer at King's College London, conducted the investigation and produced a report with recommendations designed to improve study governance across the hospital trust. Clearer guidance from both the Research and Development Department and the Research Ethics Committee was required, and slight but technically significant inconsistencies between the study design and the information listed on the IRAS project information, completed by a novice researcher, resulted in misinformation being provided at the crucial time of enquiry by the researcher.

The timing of the adverse events may have affected the decision to terminate the study early. If the adverse events had occurred later in the study, then the level of perceived risk may have been lower and the study may not have been ceased. Furthermore, it is difficult to accept that complications and adverse events in 2 out of 4 patients can demonstrate a consistent observation of surgical complications, particularly when this patient group is known to have a mortality rate of 20% per year, with mortality directly related to inflammation (Pecoits-Filho, Barany et al. 2002).

Additionally, a further 2 patients died whilst waiting to commence the study, and although these patients were to be allocated to the surgical group, they had not undergone surgery.

It is possible therefore, that the burden of co-morbidities in this patient population is responsible for the increase in perceived risk, rather than the surgical procedure itself.

There are very few studies determining the risk of different surgical procedures for haemodialysis patients. In 2 retrospective studies of perioperative mortality after abdominal aortic aneurysm repair, only 8 (0.8% of total study population) and 7 patients on haemodialysis, respectively, had undergone the procedure studied (Forbes and Lawlor 2005; Lucas, Pereira et al. 2008). Mortality varied considerably from 12.5% (Lucas, Pereira et al. 2008) to 0% (Forbes and Lawlor 2005), but it remains difficult to draw conclusions on the surgical risk in haemodialysis patients from these very small studies. Additionally, no difference in complication rates or mortality was found between haemodialysis patients and otherwise healthy patients undergoing laparoscopic cholescystectomy (Yeh, Chen et al. 2005).

More recently, it has been reported that haemodialysis patients have an increased risk of morbidity and mortality after coronary artery bypass graft surgery (Yamauchi, Miyata et al. 2012). Similarly, in patients undergoing valve surgery, elevated parathyroid hormone, serum phosphate, and calcium x phosphate product were risk factors for increased mortality in haemodialysis patients (Yan, Sharma et al. 2011). It is notable that neither of these studies was published prior to the present study commencing, and therefore were not able to be used in the assessment of risk to haemodialysis patients undertaking elective sleeve gastrectomy for weight loss.

In the time following suspension of the present study, data on the impact of kidney function on the outcomes of bariatric surgery was recently published in May 2012. Using the database of the American College of Surgeons National Surgical Quality Improvement

Program, all patients undergoing gastric bypass or gastric banding records between 2005 and 2008 were classified by eGFR to determine stage of CKD (Turgeon, Perez et al. 2012). In over 27 000 patients, almost 7 000 patients were classified as having CKD stages 2-5, including 34 patients who were already undergoing dialysis. The complication rate was almost 10% in patients with stage 5 CKD, and there was no difference in mortality between patients with and without CKD. Therefore, it is likely that the risks in sleeve gastrectomy surgery for obese patients undergoing haemodialysis are higher than in obese patients without CKD, however the level of risk is unable to be assessed in the present study, and may relate more to high cardiovascular risk, a risk factor for any major surgery, rather than that specifically related to the LSG procedure itself. Indeed, recent evidence suggest this is the case, as in a study of all non-emergent general surgery procedures, again using the database of the American College of Surgeons National Surgical Quality Improvement Program, the risk of complications and post-operative mortality was higher in patients undergoing dialysis treatment, than in non-dialysis patients undergoing the same procedures (Gajdos, Hawn et al. 2012).

Consideration of the adverse events may have been alternatively managed by recruitment suspension, as recommended by the Research Ethics Committee, and further investigation of potential risk factors undertaken, prior to further recruitment. Potential risk factors which may have been considered include the length of time patients had undergone haemodialysis treatment, pre-surgery BMI, the extent of the pre-surgery assessment including cardiac and respiratory investigations, co-morbidities and novel cardiovascular risk factors, including serum phosphate, calcium and hyperparathyroidism.

Given the experience of this investigation, several changes have been made in clinical practice to minimise risk post LSG. Factors identified during the study that may have

exacerbated risk were addressed and procedures put in place to minimise these known risks. The following changes were made to the standard care protocol to reduce the risks associated with surgery: a full "renal" assessment of each patient was to be conducted in close proximity to the surgery date; and patients are to be admitted to the renal ward under the on-call consultant nephrologist rather than to the surgical ward.

In 2011, the first report of the United Kingdom National Bariatric Surgery Registry was published. The risk of complications (2.6%) and mortality (0.1%) in obese patients undergoing bariatric surgery in the United Kingdom is very low, despite a high level of co-morbidity in the patient population (Welbourn, Fiennes et al. 2011). Presently, there is not a data field for registering CKD as a co-morbidity in the reporting forms. However, this database may present an opportunity to measure the risk of weight loss surgery in obese patients with CKD in the future, especially with the recent change to commissioning of services and the requirement that all patients are followed up for 2 years post-operatively with the data reported on the National Bariatric Surgery Registry.

Ethical issues to consider in this study

A decision to cease a research trial can be made by the Research Ethics Committee responsible for providing the favourable opinion to conduct the research, a data management committee, the study sponsor, and the research investigators. However, in this case, the research governance body at the primary study site withdrew site approval. A study may be stopped when significant differences exist between benefits and harm in the study groups, or if an excessive number of adverse events have occurred in one group (Silverman 2007). How to determine if the number of adverse events is excessive is difficult in the present study, given the relatively early cessation of the study and the known high mortality rate in this patient population, usually secondary to cardiovascular causes.

Interim assessments of clinical studies have the potential for concluding a false adverse effect (Silverman 2007), as the study denominator is undervalued. It may have been prudent to have prospectively appointed a data monitoring committee for this study, and this will be the case for any future studies using interventional procedures for weight loss in obese patients with CKD. However, if the study were to continue, this would have presented an ethical dilemma about informing the patients remaining in the study and those considering participating about the possibility of an increased risk attributable to a major surgical procedure, such as, but not limited to the LSG. Furthermore, the conflicting priorities of the researcher and the patients may also influence this decision and must be recognised (Silverman 2007). Patients should be informed of serious adverse events (Silverman 2007), however the balance of creating an informed consent process and overestimating the potential risk must be delicately handled to find equilibrium. The Information for Participants booklet did list the known risks for weight loss surgery in the general population, but did not list CKD specific risks, as there were no reported studies of LSG in haemodialysis patients. Attempts to compare the risk of this surgery with other types of abdominal surgery in patients without CKD, at the time the study was conceived, did not indicate that there was an increased risk of complications or mortality peri-operatively in patients undergoing haemodialysis compared to those not undergoing haemodialysis (Yeh, Chen et al. 2005).

Presently, the options available to obese patients with CKD on haemodialysis who are unable to be considered for kidney transplantation due to excessive BMI are limited. In patients with a BMI > 30 kg/m^2, individual assessment of risk for kidney transplantation, including assessment for cardiovascular disease, is recommended; and BMI should not be an absolute contraindication if the overall risks are tolerable, and it is perceived that mortality risk will be reduced (Dudley and Harden 2011). This view is supported by a

recent analysis of the United States United Network of Organ Sharing database, which demonstrated a significant increase in risk of delayed donor grafted kidney function with obesity, with an multivariable adjusted OR of 2.46 for patients with a BMI ≥ 40 kg/m^2 and a statistically significant, but unlikely clinically significant increase in risk of kidney graft failure of 3.6%, and no increased risk of all-cause mortality with obesity (Cannon, Jones et al. 2013). These findings question the appropriateness of BMI cut offs of 30-35 kg/m^2 for kidney transplantation. However, 1 centre in New Orleans has increased the BMI cut-off for kidney transplantation to 42 kg/m^2, with the addition of dietetic counselling for patients with a BMI of 35-42 kg/m^2 and a weight contract for patients with a BMI 40-42 kg/m^2, who must be losing weight at the time of an offer of kidney transplantation. Patients with a BMI > 45 kg/m^2 are referred for weight loss surgery prior to kidney transplantation waitlisting (Killackey, Zhang et al. 2010).

Lifestyle weight loss treatments are potentially successful, yet require significant patient input and yield between 5-10% weight loss (MacLaughlin, Cook et al. 2010), yet this may be insufficient to reach a BMI of <35 kg/m^2 in morbidly obese patients. Very low calorie diets may be efficacious, but can be maintained in the short tem only and weight gain often occurs after cessation (Ryttig and Rossner 1995). Given that the time lag between kidney transplantation wait-listing and actual transplantation is currently over 3 years in the United Kingdom, this treatment option is not likely to be effective as patients may be removed from the transplantation waiting list if their BMI subsequently increases above the threshold. Finally, newer non-surgical obesity treatments that are inserted endoscopically, such as the intra-gastric balloon device and the duodenal-jejunal bypass sleeve, remain untested in obese patients with CKD, and may be studied in this population in the future.

Implications for future research

Many lessons have been learned during the conduct of this study, most of which were unpredicted. It became apparent after the adverse events that the level of understanding of the study from the teams supporting research was insufficient to advise and act appropriately on aspects of research governance. For novice researchers, clearer guidance on, and greater scrutiny of information provided to research ethics committees is recommended, with perhaps a research governance mentorship structure in place, over and above the academic supervision provided to novice researchers during their training.

While the design of this study fits the definition of a cohort study, the manner in which the intervention was provided approaches the characteristics of clinical trial methodology, and the blurring of this boundary was clearly problematic in this study. In future, it may be prudent to call such a study as this, in which it is not absolutely clear whether the intervention being offered is standard care or experimental, a non-randomised intervention study.

Patient choice was paramount in this study, as the risks of the procedure in the study populations were not known, and whilst attempts to make this clear were made, it is always possible to find ways to increase patient understanding of the level of unknown risk further. One way to make this clearer to the public, potential participants, research ethics committee members and research governance teams would be to identify safety as the primary study outcome. The use of safety as a primary outcome in studies of novel surgical procedures is discussed extensively in Chapter 7.

Summary and conclusions

The safety and efficacy of LSG for weight loss in obese patients undergoing haemodialysis remains unknown, as this study was ceased early. Our available results demonstrate that

the procedure induces weight loss and aids patients in meeting the BMI criteria for kidney transplantation, and that in some patients at least, the risk of adverse events and mortality, may be increased. Recent studies have demonstrated an elevated risk in haemodialysis patients undergoing heart surgery, all elective general surgery, and a 10% risk of complications in patients with stage 5 CKD undergoing other weight loss surgery procedures, than in patients without CKD (Gajdos, Hawn et al. 2012; Turgeon, Perez et al. 2012; Yamauchi, Miyata et al. 2012). Further research may be conducted to assess the risk through audit of national and international bariatric surgery registry records, prior to the conduct of any carefully planned future prospective study, and this is discussed in more detail in Chapter 7.

Chapter 5: The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with chronic kidney disease: a randomised controlled pilot study

Chapter summary

Prevention of the progression of kidney damage is the ultimate goal of treatment in patients with stages 3-4 CKD, and it has been suggested that weight loss may play a role in improving kidney function, although this has not been tested in a randomised controlled trial, and previous studies have utilised estimated, rather than true markers of kidney function only. This pilot study aimed to determine the effect of weight loss on measured kidney function in obese patients with stages 3-4 CKD. A prospective, randomised controlled pilot study was conducted to examine the effect of laparoscopic sleeve gastrectomy (LSG) weight loss surgery, compared to best medical care including dietary and physical activity modifications, on kidney function. 16 patients were recruited to the study, 3 patients withdrew after randomisation, 1 patient withdrew during the intervention period and 1 patient remained on the LSG waiting list when baseline data collection was closed. 11 patients completed the study, with 5 patients undergoing sleeve gastrectomy (SG) and 6 patients in the best medical care (BMC) group. Recruitment to a randomised trial of SG weight loss surgery compared to BMC was difficult and the waiting time for LSG was longer than anticipated. There was significant weight loss over 12 months in both groups (BMC 4% $p = 0.04$; SG 35% $p < 0.001$), and waist circumference, and body fat mass also decreased significantly in the SG group. The mean difference in weight loss at 12 months was -29kg (95% CI -36, -22); median excess weight loss was 72.6% in the SG group and 9.5% in the BMC group. Estimated kidney function significantly and consistently under-predicted measured glomerular filtration rate (mGFR) using the iohexol clearance method in all patients, with a greater bias in stage 3 CKD compared to stage 4

CKD. Kidney function improved over 12 months, with a reduction in hyperfiltration, in the SG group, but not in the BMC group. Serum adiponectin increased in the SG group compared to the BMC group at 12 months (median difference 6.1; 95% CI 1.0, 19.8), and decreasing weight was inversely associated with adiponectin ($r = -0.75$ $p = 0.008$). HOMA-IR decreased in the SG group compared to the BMC group at 12 months (median difference -7.7; 95% CI -28.8, -0.5), reflecting a reduction in insulin resistance with weight loss. There were no changes in leptin or markers of inflammation (IL-6, CRP, TNF-α) between groups at 12 months. 3 out of 4 quality of life measures improved in the SG group compared to the BMC group at 12 months. Fetuin-A, an inhibitor of vascular calcification, which rises with obesity, decreased equally in both groups after 12 months, although this decrease was not associated with any other variables in the study. There were no significant changes in metabolic syndrome or hypertension with weight loss in this study. There were 2 adverse events in the SG group and 1 in the BMC group during the study. Weight loss surgery may potentially improve kidney function, insulin resistance and quality of life in obese patients with CKD. Further studies are required to provide additional safety and efficacy data on the effects of weight loss surgery in obese patients with CKD.

Introduction

There is a paucity of robust, scientific evidence informing clinical practice in the management of obesity in patients with chronic kidney disease. Prevention of the progression of kidney damage is the aim of treatment in patients with stages 3-4 CKD, and it has been suggested that weight loss may play a role in improving estimated kidney function (Navaneethan and Yehnert 2009), although this has not been tested in a randomised controlled trial. Additionally, all patients with CKD have an elevated risk of

developing cardiovascular disease, compared to the general population. The results in Chapter 2 demonstrated a relationship between participation in the Weight Management Programme (WMP) and a longer mortality and cardiovascular morbidity event-free period. This indicates that there may be a protective element associated with a programme of an energy reduced diet, increased physical activity and pharmacotherapy, however the effect of weight loss alone, such as that achieved through weight loss surgery, on cardiovascular outcomes in obese patients with CKD remains unknown. Along with examining the effect of weight loss on kidney function, this study will also attempt to characterise the relationships between weight loss and changes in inflammatory markers and adipokines, both of which are novel cardiovascular risk factors also associated with CKD (Dogra, Irish et al. 2006; Addabbo, Mallamaci et al. 2007).

This chapter describes a prospective, randomised controlled pilot study designed to compare the effect of 2 weight loss treatment strategies, LSG weight loss surgery or best medical treatment - including lifestyle modifications and anti-obesity medication, on kidney function.

Research question: Does weight loss achieved with weight loss surgery improve kidney function and modify novel and traditional cardiovascular disease risk markers in morbidly obese patients with chronic kidney disease?

Study Aims

Aim: This randomised, controlled, parallel-design pilot sutdy aimed to evaluate the effect of LSG weight loss surgery on kidney function, compared to best medical treatment, including a structured multidisciplinary WMP, in obese patients with CKD (BMI 35 - 45 kg/m^2).

Secondary aims included studying the effect of weight loss surgery on measures of quality of life and monitoring surgical complications and adverse events. Furthermore the effect of weight loss on reducing insulin resistance, hypertension, dyslipidaemia, inflammation and the adipokine response was studied, to determine whether weight loss reduced the cardiovascular burden associated with obesity and CKD in this patient group.

Primary Hypothesis

Weight loss following SG improves kidney function (in obese patients with stages 3-4 CKD, compared to BMC including a structured lifestyle based weight loss intervention, including dietary modification and increased physical activity, and anti-obesity medication.

Primary Outcome

The primary outcome measure was measured GFR (ml/min) using the iohexol clearance method 12 months post SG, compared to BMC.

Determination of GFR is considered the gold standard for assessing kidney function, when measured using an inert substance which is cleared exclusively from the body by glomerular filtration. Iohexol, is such a substance, and is an iodine based, non-ionic, radiological contrast agent, cleared exclusively by the kidneys. Measurement of plasma iohexol clearance over time is considered a gold standard technique (Niculescu-Duvaz, D'Mello et al. 2006) as it correlates well with classical gold standard methods such as inulin or chromium-51 labelled ethylene diamine tetracetic acid (EDTA) clearance (O'Reilly, Brooman et al. 1986; Brown and O'Reilly 1991), although evidence of such comparisons in obese patients with CKD is lacking. Indeed, there is a paucity of evidence on the use of iohexol measured GFR in obese subjects or obese patients with CKD.

As kidney function declines, determination of GFR using iohexol clearance can take up to 5 hours, which is expensive and inconvenient to measure in a clinic. Fingertip blood sampling onto blotting paper correlates well with serum sampling techniques (r^2=0.953), and it is suggested that use of this technique allows patients to complete the test at home, with samples being returned in the post (Niculescu-Duvaz, D'Mello et al. 2006; Mafham, Niculescu-Duvaz et al. 2007). This method reduces the time patients are required to attend a hospital or clinic for the measurement of kidney function, and appears to be a practical and efficient method of measuring GFR for both patients and the researcher. Results of this method with patients actually performing their own fingertip blood sampling, compared to results obtained by researchers in a laboratory setting, have not been published. Similarly, there are no data on the use of this method for repeated measures of GFR longitudinally. Therefore, the utility of the method of GFR measurement, as much as the effect of the treatment on GFR itself, was explored in this study.

Use of an exogenous marker that is cleared almost exclusively by the kidneys may eliminate problems associated with the measurement of changing kidney function with weight loss, as body composition changes. GFR can be expressed relatively, after correction and standardisation for body surface area (ml/min/1.73m^2) or in absolute terms (ml/min). As changes in body surface area with weight loss affect the relative GFR, regardless of change in actual kidney function, absolute GFR, rather than relative GFR, was selected for use in this study (Delanaye, Radermecker et al. 2005). Similarly, as muscle mass may decrease with weight loss alongside a decrease in fat mass, changes in estimates of GFR that are based on serum creatinine or cystatin-C (the former a product of muscle breakdown, and the latter produced in all nucleated cells, including adipocytes) are also unsuitable for use in this study, as changes in body composition are expected to occur (Jesudason and Clifton 2012).

Secondary Hypotheses and Secondary Outcomes

1. **Weight loss following laparoscopic sleeve gastrectomy resolves or improves co-morbidities including type 2 diabetes, insulin resistance, hypertension, proteinuria, hyperlipidaemia, and metabolic syndrome, compared to best medical care - including a structured lifestyle based weight loss intervention and anti-obesity medication.**

Insulin resistance (HOMA-IR), type 2 diabetes, blood pressure, blood lipids and metabolic syndrome

Insulin resistance, hypertension and dyslipidaemia are elements of metabolic syndrome, which is associated with both CKD and obesity (Wahba and Mak 2007; Sarafidis 2008). Weight loss in obese patients without CKD is known to improve all three factors (Klein 2001; Bougoulia, Triantos et al. 2006), yet there is little information on the effect of weight loss on these parameters in obese patients with CKD. Previous research has demonstrated that multidisciplinary, targeted interventions in patients with stages 3-4 CKD - which were not specifically aiming for weight loss - can have positive effects on BP, dyslipidaemia, progression to kidney failure, and outcomes up to 2 years after the commencement of renal replacement therapy (Levin 2001).

HOMA-IR is a validated model of estimating insulin resistance from steady state insulin and glucose concentrations, calibrated to give a normal insulin resistance equal to 1 using the estimation equation (Matthews, Hosker et al. 1985). HOMA-IR correlates with insulin resistance, measured by the standard glucose clamp method, in patients with CKD (Shoji, Emoto et al. 2001). Patients with CKD,

without diabetes, have HOMA-IR scores 3 times higher than healthy controls, (mean HOMA-IR 2.9 (95% CI 2.4 to 3.5, vs 1.0 (95% CI 0.8 to 1.2), $P < 0.001$) (Dogra, Irish et al. 2006), even in the earliest stages of CKD when GFR is normal and when patients with CKD and healthy controls are matched for body weight (Becker, Kronenberg et al. 2005). HOMA-IR is approximated as (fasting plasma insulin mU/L x fasting plasma glucose mmol/L) divided by 22.5, however, the mathematical model includes more sophisticated modelling to better replicate the physiology, particularly in more hyperglycaemic states (Levy, Matthews et al. 1998). There is no information on the effect of weight loss on insulin sensitivity in obese patients with CKD. In obese women without CKD, insulin sensitivity improved with weight loss and was also related to favourable changes in adiponectin, free fatty acids (Esposito, Pontillo et al. 2003) and albuminuria (Gilardini, Zulian et al. 2010).

Hypertension and decreased HDL cholesterol are associated with the development of CKD (Fox, Larson et al. 2004), and elevated systolic BP is associated with CKD progression in patients with co-existing albuminuria (Yan, Zhu et al. 2012). Hypertension is highly prevalent in obese patients with CKD, despite management with multiple anti-hypertensive medications (MacLaughlin, Sarafidis et al. 2012).

Urinary albumin-to-creatinine ratio and protein-to-creatinine ratio

Albuminuria and proteinuria decrease with weight loss in both the general population and in obese patients with CKD (Bello, de Zeeuw et al. 2007; Agrawal, Krause et al. 2009; Navaneethan, Yehnert et al. 2009; Afshinnia, Wilt et al. 2010). Reduction in albuminuria is related to changes in CRP, BP, lipids and blood glucose, but remains independently associated with weight loss after adjustment for

these associations (Bello, de Zeeuw et al. 2007). The impact of weight loss on proteinuria and albuminuria, both known cardiovascular disease risk factors, may be related to reductions in lipotoxicity, inflammation and oxidative stress, as well as changes in BP, blood lipids and blood glucose control, indicating that a mix of traditional and novel cardiovascular disease risk factors are involved (Afshinnia, Wilt et al. 2010).

2. **Quality of life scores improve and anxiety and depression scores decrease following laparoscopic sleeve gastrectomy, compared to best medical care.**

As decribed in Chapter 4, the self administered Short Form 36 (SF-36) and Hospital Anxiety and Depression Scale (HADS) (Appendix B) are widely used and validated measures of aspects of quality of life. Weight loss surgery is associated with improved quality of life in most, but not all studied populations (Ballantyne 2003). Quality of life is an important measure to aid future clinical treatment decisions. If quality of life improves with weight loss, regardless of other outcome measures, the intervention treatment may be worth pursuing for perceived patient benefit alone.

3. **Fat mass (derived from bioelectrical impedance analysis) and waist circumference decrease following laparoscopic sleeve gastrectomy and patients remain well nourished (measured by Subjective Global Assessment), compared to best medical care.**

Body composition (weight loss (kg), percentage excess weight and BMI loss, waist and hip circumference, lean body mass and body fat mass measured with multi-frequency bioelectrical impedance analysis)

Absolute weight loss is the difference between baseline weight and weight at the time-point of measurement, calculated as an absolute value and also as a percentage of baseline weight. Excess BMI loss is calculated as the percentage of weight lost from the difference between actual body weight and body weight at a BMI = 25 kg/m^2, calculated as % excess BMI loss = [absolute weight loss/(baseline weight – weight if BMI = 25 kg/m^2)] x 100. Absolute weight loss as a percentage of baseline weight, and excess BMI loss are the preferred reportable standards for weight loss (Deitel, Gawdat et al. 2007), however excess weight loss has also been calculated and reported as a comparator to previous studies. Excess weight loss is the most reported weight loss parameter for weight loss surgery, and is determined from the midpoint of the 1983 Metropolitan Life Insurance Tables for medium build, and calculated as % excess weight loss = [Absolute weight loss/difference between baseline weight and the mid point of the 1983 Metropolitan Life Insurance Tables for medium build)] x 100 (Deitel, Gawdat et al. 2007).

Lean body mass is calculated as body weight minus fat mass. Fat mass is estimated from the relative resistance to an electrical signal as a function of body weight and height (adjusted for age and gender) using a multi-segmental body composition analyser (Biospace Inbody 720 analyser; Korea). Assessment of body composition using multiple frequency bioelectrical impedance analysis demonstrated good agreement with dual-energy x-ray absorptiometry assessment of lean and fat mass during weight loss, in a study of obese and overweight women (Thomson, Brinkworth et al. 2007). There are no published studies using bioelectrical

impedance to monitor body composition changes with weight loss in obese patients with CKD.

Waist to hip ratio is related to cardiovascular disease risk (MI and fatal coronary disease) in patients with CKD (Elsayed, Tighiouart et al. 2008). Waist circumference and waist to hip ratio provide alternative measures of body fat distribution to BMI, which is elevated when lean body mass is greater than normal, overestimating obesity.

4. **Adipokines and markers of inflammation improve with weight loss following laparoscopic sleeve gastrectomy, compared to best medical care. A reduction in leptin, IL-6, TNF-α, hs-CRP, and fetuin-A, and an increase in adiponectin, is predicted with weight loss.**

An increase in adiponectin and a reduction in leptin, CRP and IL-6 occur with intentional weight loss in obese subjects (Gallistl, Sudi et al. 2001; Esposito, Pontillo et al. 2003; Kelesidis, Kelesidis et al. 2010). With weight loss in obese patients with CKD, it is predicted that changes in leptin and adiponectin will reflect changes in adipocytes, and changes in IL-6 and TNF- α will reflect changes in an immune-modulated response from macrophages. Fetuin-A is related to insulin resistance and metabolic syndrome characteristics, and decreases with weight loss, which may be associated with improved insulin resistance and an increase in adiponectin (Ix, Chertow et al. 2006; Reinehr, Roth et al. 2008; Ix and Sharma 2010).

Methods

Study Design

This study was a prospective randomised controlled pilot study of SG weight loss surgery compared to BMC (Figure 14). Patients were allocated to treatment groups in a 1:1 ratio.

Ethical Review and Research Governance

This study followed the principles of the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (World Medical Association 2008), and was approved by the London Surrey Borders Research Ethics Committee in November 2009 (09/H0806/69). All study patients provided written informed consent. King's College Hospital Research and Development governance approval was granted in January 2010, followed by approval from St Helier Hospital and Guy's and St Thomas' Hospital. The study was registered in the Clinical Trials.gov registry with the unique trial number NCT01053130.

A study protocol amendment was made to send letters of invitation to all patients meeting study criteria, and the Research Ethics Committee approved this on March 26, 2010.

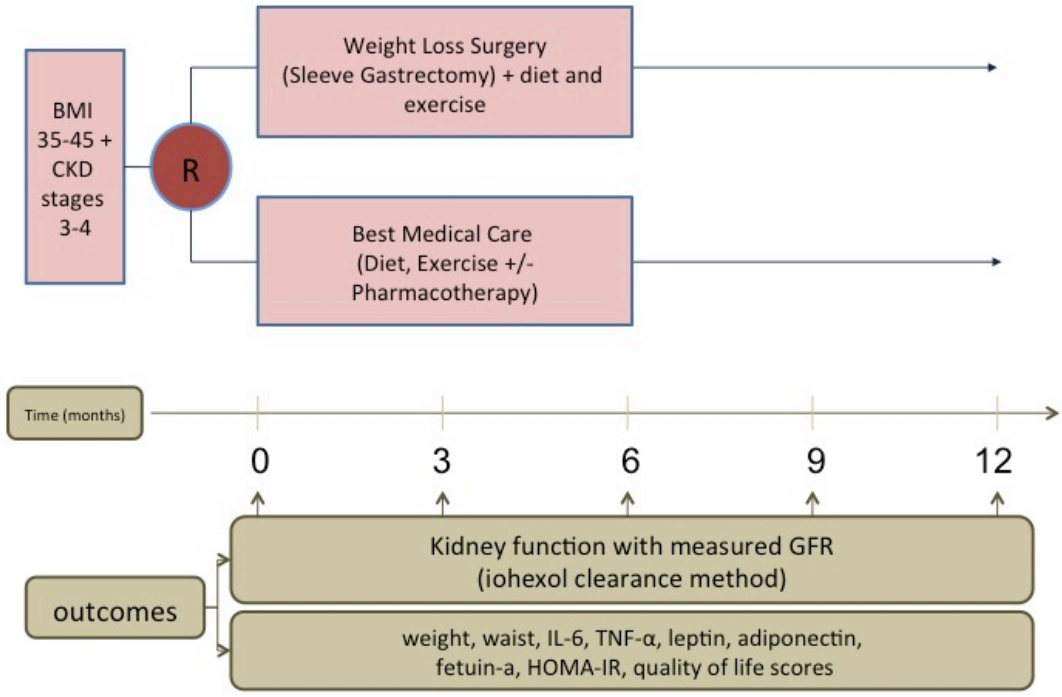


Figure 14: Schematic representation of study design and outcomes for the weight loss surgery in stages 3-4 chronic kidney disease (CKD) randomised controlled pilot study

BMI, body mass index; GFR, glomerular filtration rate; HOMA-IR, method of homeostasis assessment for insulin resistance; IL-6, interleukin-6; R, randomisation; TNF-a, tumour necrosis factor-α

Recruitment of patients

The recruitment period commenced in March 2010 and continued until June 2011.

Patients were recruited from outpatient clinics at all 3 study sites.

Preliminary Screening

Existing hospital patient databases and out-patient clinic appointment lists were searched for patients meeting the primary inclusion criteria of >18 years, BMI 35 - 45 kg/m^2, and eGFR of 20 - 60ml/min/1.73m^2. The candidate is a Registered Dietitian with extensive clinical experience with CKD patients, and obtained permission to access clinical records and talk to patients at NHS sites hosting the research study. Additionally, the candidate attended out-patient clinics to screen patients using the above criteria after height and weight measurements were taken, when this information was not available in existing

databases. Patients meeting these criteria were then assessed against the full study inclusion and exclusion criteria (Table 18) from information in the patient's medical record. Nephrologists from participating hospitals also referred potential participants for the study.

Table 18: Inclusion and exclusion criteria for patient participation

Inclusion criteria	Exclusion criteria
Male or female, aged > 18 years	Pregnancy
Previously attempted weight loss	History of chronic liver disease
BMI 35-45 kg/m^2	Previous bariatric surgery, gastric surgery or large hiatus hernia
Estimated glomerular filtration rate 20-60ml/min/1.73m^2 using the 4 variable modified MDRD study prediction equation	Psychiatric illness including anxiety, mood and untreated eating disorders
	Malnutrition (assessed by Subjective Global Assessment)
	Infection or course of antibiotics within the last month
Written informed consent	Unfit for anaesthesia or surgery
	Unwilling to consider surgical treatment
	Previous kidney transplant

BMI, body mass index; CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease study

All patients meeting the study inclusion criteria were then sent a letter of invitation to participate in the study, together with a form letter to complete and return in the enclosed reply paid, pre-addressed envelope, if they were interested in obtaining further information about the study.

Patients who indicated they were interested in participating in the study by returning the form were contacted to arrange an individual appointment to further discuss the study. At this appointment, the candidate explained the random allocation procedure and both study interventions to the potential participants. Both the weight loss surgery procedure and the best medical care interventions were explained to potential participants, including the amount of weight loss expected with each, the number of study visits, and what was involved in each of the study measurements. The risk of each study measurement was outlined. Potential participants were given the opportunity to ask questions and were

provided with written Information for Participants (Appendix E). The candidate also emphasised that participation was voluntary, and that the participant was free to withdraw from the study at any time, without their medical care being affected. Patients decided at this point whether they were interested in taking part and could be contacted again by telephone 1-2 weeks later.

Final Recruitment

Patients interested in pursuing the study further were referred to the study surgeon for assessment for LSG. A member of the surgical team completed the assessment, and the dietitian (the candidate) conducted an additional dietary assessment for weight loss surgery (Appendix D). Patients were referred for additional cardiovascular and respiratory assessments and further surgical review, if deemed appropriate, prior to being assessed as fit or unfit for weight loss surgery. If the patient was assessed as fit for surgery and agreed to participate in the study, written, informed consent was obtained. Patients unsure whether they wished to participate were given more time to consider the study, and the candidate contacted the patient again after a mutually agreed time interval.

Consent

The process and meaning of informed consent was discussed, including the right to withdraw from the study at any time without compromising the patient's medical care. It was the responsibility of the person obtaining informed consent to assess capacity, ensure that they were satisfied that the patient understood the content of the Information for Participants booklet (Appendix E), the meaning of randomisation to treatment, and the right to withdraw. If the patient was willing to participate in the study, the candidate, the study surgeon, or the patient's named nephrologist, obtained written informed consent. 1 copy of the consent form (Appendix E) was given to the patient, 1 copy was filed in the

medical notes, and the original consent form was filed in the study master file, together with a copy of the patient information booklet. All members of the study team and medical care team had undertaken consent training and were able to assess capacity to consent.

Randomisation

After providing informed consent to participate in the study, each patient was randomised to 1 of the 2 study interventions. Patients were assigned to either SG or BMC using a concealed random allocation method. An independent professional not involved with the trial held the computer generated random allocation sequence generated using permuted blocks of 2 - 4. After each consecutive patient provided consent, the candidate contacted the sequence holder by telephone to be informed of the next allocation in the sequence. Each patient was notified of his or her allocation by the candidate, within 3 days of providing consent to participate in the study.

Interventions

Best Medical Care (BMC)

All patients randomised to the BMC treatment group were enrolled in the renal Weight Management Programme (WMP). There are 4 components to the multi-disciplinary WMP: a low-fat energy-reduced renal diet, regular exercise, behaviour therapy, and use of the anti-obesity medication orlistat (Xenical; Roche Products, Basel, Switzerland). An experienced renal dietitian and physiotherapist conducted the programme, with support from the nephrologist and renal pharmacist as needed. Patients attended the WMP for the initial baseline assessment, monthly during the 6-month intervention period, and for monitoring and support at 9 and 12 months. Individualised diet and exercise regimens were developed with all patients using structured dietary education with motivational interviewing (Miller

and Rollnick 2002) and cognitive behavioural therapy techniques to address barriers to lifestyle change; including food and activity diaries, stimulus control, through process evaluation, cost benefit analysis, and problem solving (Cooper, Fairburn et al. 2003). Treatment was structured and standardised, with checklists for each session developed to act as both cue for, and record of, the session.

Dietary Intervention

A low-fat energy-reduced 1 400 – 1 800 kilocalorie renal diet, depending on body size, physical activity level and dietary intake at baseline, was negotiated with each patient based on food preferences and appropriate for each patient's CKD stage. Protein intake was optimised for the stage of CKD for each patient, at 1.0 g protein/kg ideal body weight (IBW)/day for CKD stage 3 and 0.8-1.0g protein/kg IBW/day for CKD stage 4 (EDTNA/ERCA Dietitians' Special Interest Group 2002). Fat intake was limited to less than 70 g per day, to minimise the side effects of orlistat. The remaining energy was obtained from carbohydrate sources, with higher fibre choices encouraged when possible. All patients were encouraged to modify sodium intake to a "no added salt" diet level, of 80 - 100 mmol sodium per day (EDTNA/ERCA Dietitians' Special Interest Group 2002). Potassium and phosphorous intake were modified according to serum biochemistry and kidney function (Abbott, Glanton et al. 2004; Renal Association 2007). Adherence to the dietary intervention was assessed with 3-day food intake records at baseline and every 3 months. At each visit, dietary education was provided, as required, using a range of standardised modules (Table 19) with picture based resources and written information. Patients generated at least 2 dietary goals each month from baseline to month 6, facilitated by motivational interviewing techniques used by the dietitian (Miller and Rollnick 2002).

Table 19: Standardised dietary education modules in the renal Weight Management Programme

Size Matters – portion control	Identifying high risk situations
Eating a low fat diet	Meal Plan
Low fat cooking + quick recipes booklet	Problem solving techniques
Eating Out	Keeping going

Exercise Intervention

Personal exercise plans, developed from the patient's individual current level of exertion and co-morbid conditions, incorporated both aerobic and muscular endurance activities to improve functional capacity and increase energy expenditure. Frequency was at least 3 days each week, the duration was increased, as tolerated, up to 60 minutes each day, and the intensity was based on the Borg Scale for ratings of perceived exertion levels of *somewhat hard* to *hard* (Borg 1998). The exercise plan was adapted at each monthly visit in line with improvements in exercise capacity to facilitate a progressive training effect.

Pharmacotherapy

Patients were offered orlistat at the standard dose of 120 mg 3 times a day (taken with each meal) during the study. Orlistat is a locally acting gastrointestinal lipase inhibitor that reduces the absorption of dietary fat by approximately 30% (Guerciolini 1997). On-going education about the mechanism of action and the importance of limiting dietary fat intake to reduce the gastrointestinal side effects associated with the drug's inhibition of dietary fat absorption was provided.

Approximately 12 months after the study commenced, the manufacture of orlistat was temporarily halted, due to a manufacturing problem, and supply of the medication ceased soon afterwards. Patients were unable to obtain orlistat from this point until the completion of the study.

Laparoscopic Sleeve Gastrectomy Weight Loss Surgery (SG)

Patients randomised to the SG treatment group underwent laparoscopic sleeve gastrectomy. SG as a primary procedure consisted of a subtotal gastric resection of the fundus and body, to form a tube like stomach along the lesser curvature, with a final volume of 100 - 200ml (Iannelli, Dainese et al. 2008). The surgery was performed by an experienced minimal access surgeon, Mr Ameet Patel, who had already performed at least 50 sleeve gastrectomies. Resected tissue samples were examined for evidence of helicobacter pylori and treatment with a proton pump inhibitor and antibiotics was commenced if positive.

Post Surgery Dietary Intervention

Patients were provided with dietary education and renal-specific written information prior to the procedure, or 1-2 days post-procedure as an inpatient. Dietary intake was reviewed at 1, 4, 6 and 12 weeks post-sleeve gastrectomy, then at 3-monthly intervals up to 12 months. Dietary intake progressed in texture from liquid to puree, then to soft foods over 12 weeks, before finally re-introducing most normal foods between 4 - 6 months post-surgery. Volume of food or fluid intake was limited to 100 - 150 ml per meal, up to 6 times a day, with frequent sips of fluid encouraged. This level of intake is sustainable due to the reduced stomach volume. Intakes greater than 150ml at a time may stress the suture line and create a leak, or stretch the surgically reduced stomach capacity, increasing the risk of compromising the physical restriction imposed by the surgery - which may impede weight loss or result in weight gain.

Dietary energy intake was restricted to approximately 1 000 kcal per day post sleeve gastrectomy. Protein intake was optimised for the stage of CKD for each patient, at 1.0 g protein/kg IBW/day for stage 3 CKD, and 0.8 - 1.0 g protein/kg IBW/day for stage 4

CKD (EDTNA/ERCA Dietitians' Special Interest Group 2002). The remaining energy was obtained from carbohydrate and fat sources, with low fat choices strongly encouraged. Patients were also recommended to enjoy a wide variety of tolerated foods. All patients were encouraged to modify sodium intake to a "no added salt" diet level, of 80 - 100 mmol sodium per day (EDTNA/ERCA Dietitians' Special Interest Group 2002). Potassium and phosphorous intake were modified according to serum biochemistry and kidney function (Abbott, Glanton et al. 2004). A daily multivitamin and mineral supplement suitable for patients with CKD was prescribed.

Measurements

A brief description of all measurements is included here, and an in-depth description of those measurements that require a specific method of measurement or technique is outlined in Appendix D. To provide an overview of the data collection procedure, an outline of a study visit is presented in Figure 15.

A timetable of study and data collection visits for both intervention groups is provided in Table 20.

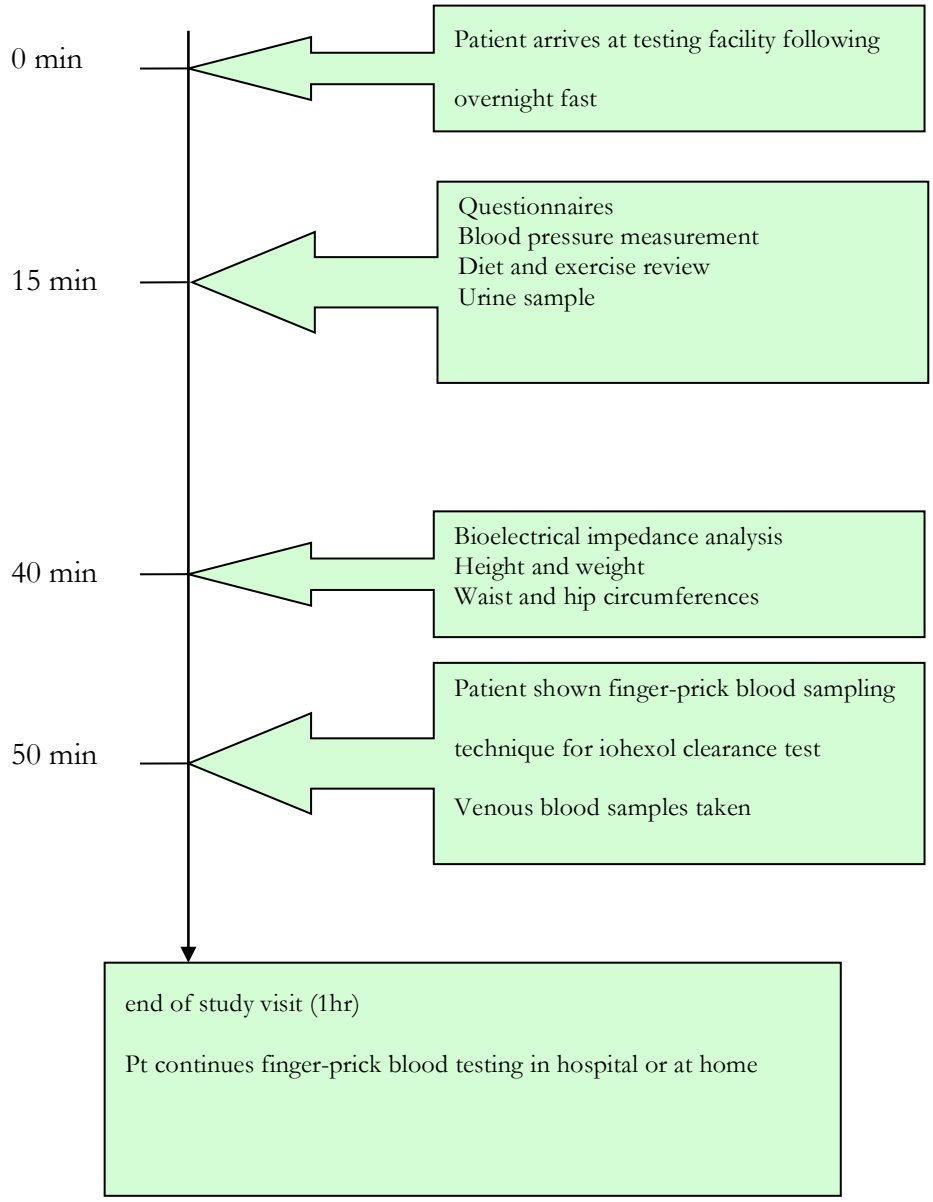


Figure 15: Outline of study visit at baseline, 6 and 12 months for the weight loss surgery in the stages 3-4 chronic kidney disease randomised controlled trial pilot study

Demographics

Baseline demographic data including date of birth, ethnicity, gender, and cause of CKD (if known) was recorded at study enrolment. History of diabetes, cardiovascular disease, hypertension, dyslipidaemia, surgical history and body weight history (including attempts at weight loss) were recorded at baseline. Medications, including daily or weekly doses, were recorded every 3 months.

Table 20: Timetable of intervention and data collection visits for the weight loss surgery in the stages 3-4 chronic kidney disease randomised controlled trial pilot study

	Best Medical Care (BMC)	Sleeve Gastrectomy (SG)
Month	**Pre assessment**	
Date	**Including assessment for surgery and completion of 3 day food and exercise diary**	
0	**Study visit 1: baseline (beginning) data collection**	
	Weight management clinic 1st appointment	**Surgery – laparoscopic sleeve gastrectomy** **Post operative surgical review** **dietary reviews by telephone**
1	1 month review	**dietary review by telephone**
2	2 month review	**dietary review by telephone**
3	**Study visit 2: 3 month review + data collection**	
4	4 month review	-
5	5 month review	-
6	**Study visit 3: 6 month review + data collection**	
9	**Study visit 4: 9 month review + data collection**	
12	**Study visit 5: 12 month review + data collection**	

Laboratory assessments

Venous blood samples were collected in blood collection tubes (BD Vacuainer: New Jersey) after a 12-hour fast. Multiple samples were collected in EDTA-coated tubes for full blood count and plasma extraction, fluoride oxalate-containing tubes for plasma glucose, and silica-coated serum-separating tubes for serum leptin, adiponectin, fetuin-A, IL-6, TNF-α, lipids, hs-CRP, and insulin.

The sample for plasma was centrifuged upon arrival in the laboratory, and the samples for serum were left for 30 minutes to clot before being spun. Samples for glucose, hs-CRP, full lipid profile, and a full blood count were processed immediately, and the remaining serum and plasma was stored in aliquots at -80° C for later analysis of serum leptin, fetuin-

A, adiponectin, IL-6, TNF-α, and insulin. Spare aliquots of serum and plasma were stored in case further biomarkers were added to the study at a later date. The Renal Association targets for total cholesterol and low density lipoprotein (LDL) cholesterol were used to classify a reduction in dyslipidaemia (Renal Association 2007).

Serum leptin, fetuin-A, adiponectin, hs-CRP, insulin, IL-6 and TNF-α were measured using commercially available quantitative sandwich enzyme-linked immunosorbent assays (ELISA) (R and D systems, Minneapolis, MN) in the King's College Hospital Biochemistry Laboratory, under the supervision of Professor Roy Sherwood. Standard enzymatic techniques were used to measure lipid fractions and total cholesterol. Glucose was measured in venous fluoride EDTA plasma using standard enzymatic techniques. HOMA-IR was used to calculate an index of insulin resistance from the product of the fasting concentrations of plasma insulin (microunits/ml) and plasma glucose (mmol/l) divided by 22.5 (Matthews, Hosker et al. 1985). Given that insulin resistance is evident in CKD even at normal body weight and without diabetes, a HOMA-IR level ≥ 2.0 was selected to indicate insulin resistance in the present study.

Patients were asked to provide a urine sample in a universal container. The sample was sent to the biochemistry lab with the blood samples for analysis of protein-to-creatinine ratio (proteinuria) and albumin-to-creatinine ratio (albuminuria), according to standard clinical methods. Clinically significant proteinuria and albuminuria were defined according to the National Institute for Health and Clinical Excellence (NICE) clinical guidelines for CKD (CG73), as > 50 mg/mmol and > 30 mg/mmol, respectively, in people without diabetes. In those with diabetes, albuminuria was defined as > 2.5 mg/ mmol in women or > 3.5 mg/mmol in men as these levels are considered clinically significant (National Institute for Health and Clinical Excellence 2008).

Kidney function was measured by GFR using the gold standard iohexol clearance method, with finger-prick blood sampling (Appendix D). Iohexol is an iodine- containing contrast medium that is not metabolised and has no uptake in tissue. After injection, iohexol is rapidly distributed throughout the extracellular fluid and excreted almost exclusively by the kidneys via glomerular filtration (Stevens and Levey 2009). Briefly, timed fingerprick blood samples were taken before and 2, 3, and 4 hours (5 hours if eGFR < 30ml/min/1.73m^2) after administration of a 5ml bolus of iohexol. The patient took the fingerprick sampling kit home to complete the test and returned the equipment in the pre-addressed, pre-stamped envelope provided.

Nutrition assessment

Adherence to dietary guidelines was assessed with 3-day food intake records with dietary interviews to clarify and substantiate the content at baseline and every 3 months. Nutritional status was measured with Subjective Global Assessment - a validated tool assessing nutritional status with information on weight loss, dietary intake, gastrointestinal symptoms, physical capacity and muscle and fat stores (Detsky, Mclaughlin et al. 1987).

Anthropometry

Height was measured to the nearest 1 cm without shoes using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg on a calibrated electronic scale with the patient wearing light clothing and without shoes. Waist and hip circumferences were measured to the nearest 0.1 cm at the level of the umbilicus and the widest point around the buttocks, respectively, with a calibrated plastic tape measure.

Fat mass, percentage body fat and fat free mass were measured using multi-frequency, multi-segmental bioimpedance analysis with the In Body 720 analyser (Biospace Ltd, Korea).

Other measures

BP was measured with the patient seated in a chair and rested for at least 10 minutes, with 3 measures made using an appropriate-sized cuff. The average of the 2 closest readings for systolic BP were used. Hypertension was defined using the NICE guidance for CKD criteria of a blood pressure > 140/90 mm Hg, or > 130/80 mm Hg in those with proteinuria or diabetes (National Institute for Health and Clinical Excellence 2008), or use of antihypertensive medications, including diuretics. Antihypertensive medication use was scored according to type and dose of medication, using the Antihypertensive Score (AHS) method (Fricke, Doehn et al. 1998; Meier, Nitschke et al. 2006), and statin doses were also recorded, at baseline, and up to 12 months.

Quality of life was measured using the self adminstered HADS and SF 36 questionnaires.

Metabolic syndrome was assessed according to the revised ATP III criteria (Grundy, Cleeman et al. 2005).

Predefined complications of weight loss surgery included poor tolerance of liquids/puree/soft diet, gastrectomy leak, bleeding requiring transfusion, bleeding or restriction requiring surgical or endoscopic intervention, longer than expected hospital admission, readmission to hospital directly related to weight loss surgery, post-operative infection, and 30 day mortality; and were recorded as soon as they became known to the study team.

Adverse events, including acute kidney injury, cardiovascular events including myocardial infarction, stroke and hospitalisation for heart failure, gastro-oesophageal reflux, heart rhythm irregularities, malnutrition, dehydration, vomiting, hypoglycaemia, diarrhoea, constipation, epigastric pain and oedema and hospitalisation during the study period, were reported and recorded at study visits.

Statistical Analysis

Sample size calculation

The sample size was calculated for detecting a difference in measured kidney function at 12 months, based on the results of an observational study of change in estimated kidney function following weight loss surgery in a small group of patients with stage 3 CKD (Navaneethan and Yehnert 2009). The sample size was estimated using the following assumptions: 12 months duration of follow-up; maintenance of kidney function in the control group at 12 months, and an improvement in kidney function of 18% (SD 10.2%) in the study group at 12 months (based on the improvement in eGFR observed in obese patients with stage 3 CKD after weight loss surgery (Navaneethan and Yehnert 2009)); 80% power to detect a 5% significance level. Allowing for a 20% drop out rate, the sample size required was 27 patients randomised to SG and 27 patients randomly allocated to BMC.

This sample size was deemed impractical given the constraints of capacity for elective surgery at the study hospital, current waiting times for weight loss surgery (which can be up to 12 months), and the human resources available to conduct the study. The candidate was the only person working on screening, recruitment, data collection and providing the

dietetic components of both interventions to all study participants. Therefore, a pilot study was conducted, which aimed to recruit a total of 16 patients (8 per group). It was deemed appropriate to conduct a pilot study of this size to examine the feasibility of recruiting to a randomised study surgical treatment compared to medical care, to determine the effect size of changes in measured kidney function, markers of inflammation and adipokines, and to monitor the frequency and types of adverse events and surgical complications.

Data analysis

Expert statistical advice from a statistician, Dr Salma Ayis, Lecturer in Medical Statistics, King's College London, was sought prior to, and continued throughout, the pilot study. Comparative statistical analyses using quantitative data were performed using IBM SPSS Statistics version 19.0. The normality of data distribution was assessed visually using histograms with normal curves. For non-normally distributed data, due to the small sample size, log transformation was not performed, and non-parametric statistical methods were adopted.

Baseline data are described as mean ±SD (median and inter-quartile range (IQR) for non-parametric distributions) for all continuous outcome variables. Event rates of categorical variables within and between groups were listed in contingency tables. Changes in variables over time are displayed as means (95% CI), or median (IQR). The difference in body composition measures, markers of inflammation and adipokines, within groups from baseline to 12 months were measured with paired Student's t-tests, and the between group differences at 12 months were determined with the Mann-Whitney U test, Hodges-Lehman median difference, or with analysis of variance between groups at 12 months with correction for baseline values, with 95% confidence interval reported for differences

between groups. Differences in adipokines and markers of inflammation were calculated for exploratory purposes only, as it was known at the outset of the study that it was unlikely that the sample size would be adequate to detect differences in these variables. Differences in diabetes, insulin resistance, hypertension, proteinuria, hyperlipidaemia and metabolic syndrome over time are described empirically.

Given the small sample size in this pilot study, relationships between variables were examined with Spearman's rank correlation, to explore the associations between weight loss, and changes in adipokines, markers of inflammation, and measures of body composition. The relationship between measured GFR and eGFR using the MDRD study equation at baseline, 6 and 12 months, was examined with Spearman's rank correlations.

Complications and adverse events were collated and analysed descriptively.

Results

Study Participants

The flow of participants through each stage of the study is shown in Figure 16. During the 15-month recruitment period, 182 patients at the 3 study sites met the preliminary inclusion criteria and were contacted either by letter or during a scheduled outpatient clinic visit.

93 patients expressed an interest in the study and were given the patient information booklet, which outlined both intervention treatments, and the random allocation process was explained in both written and verbal forms. 51 patients declined to participate and a further 10 were excluded, and 35 patients underwent surgical assessment.

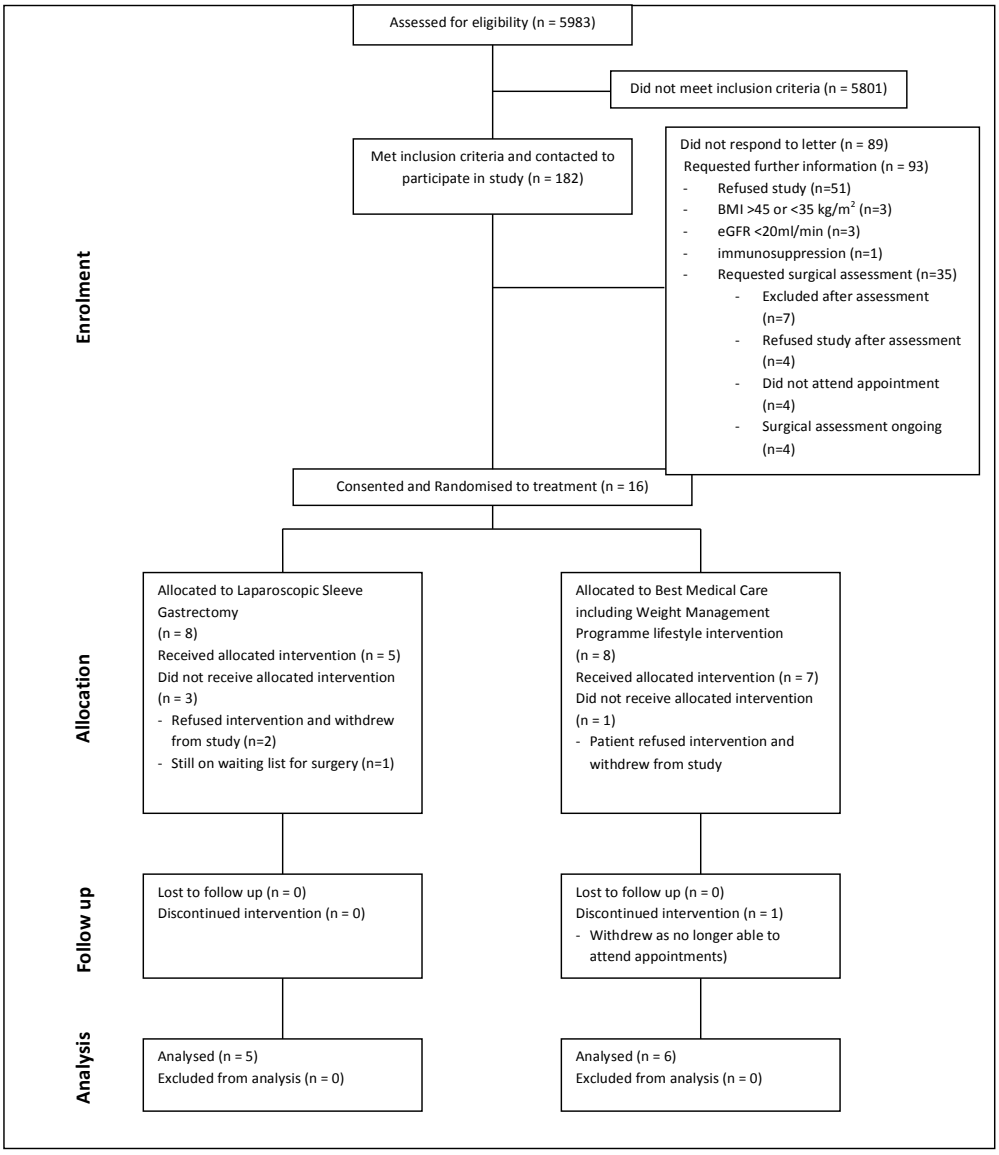


Figure 16: CONSORT diagram showing the flow of participants through each stage of the Stages 3-4 Chronic Kidney Disease randomised controlled trial pilot study of laparoscopic sleeve gastrectomy compared to best medical care

BMI, body mass index; eGFR, estimated glomerular filtration rate

The mean (± SD) length of time between requesting a surgical assessment appointment and obtaining consent was 3 months (± 1.48 months). 7 patients were excluded prior to obtaining consent, as they were assessed as unsuitable for weight loss surgery, due to co-morbidities including hiatus hernia, previous abdominal hernia repair with mesh insert,

bipolar disorder, or unsuitable for anaesthesia; 1 patient was a Jehovah's Witness, and so was deemed unsafe for surgery given the risk of bleeding and refusal to accept blood transfusion. 4 patients did not wish to be randomised to a treatment group after surgical assessment, and 4 patients did not attend the surgical assessment appointment, despite multiple appointments being offered. A further 4 patients were still awaiting cardiology or respiratory review as part of surgical assessment in June 2011, which was the final month when assessment could be practically completed to allow for a minimum of 3 months on the surgical waiting list and 12 months of follow up. 16 patients elected to enrol in the study and 5 of the 8 patients in the SG group and 6 of the 8 patients in the BMC group completed the study.

Recruitment and randomisation was completed by June 2011 and the final patient follow-up was in September 2012. The mean length of time from randomisation to intervention (surgery) in the SG group was 5.6 months (± 2.2 months). Overall, patients commenced the study 5.8 months (± 3.1) after the initial approach and provision of the patient information.

The baseline characteristics of the 2 groups are presented in Table 21. All patients had metabolic syndrome, and all were prescribed antihypertensive medications and a statin. There were no statistically significant differences in demographics, anthropometric, clinical and metabolic variables, although there was a tendency towards greater prevalence of diabetes and insulin resistance (HOMA-IR), and higher systolic BP in the BMC group, despite randomisation. None of these differences were statistically significant, possibly due to the small sample size. Median leptin was also higher in the BMC group, despite closely matched levels of fat mass between groups at baseline.

Table 21: Baseline characteristics of obese patients with stages 3-4 chronic kidney disease randomised to either laparoscopic sleeve gastrectomy or best medical care

Parameter	Sleeve Gastrectomy (SG)	Best Medical Care (BMC)	p*
n	5	6	
Age (years)	51 (47.5-55)	53 (46.5-66)	0.78
Gender	5 Female	4 Female, 2 Male	0.46
Ethnicity	3 White, 2 Black	3 White, 3 Black	1.00
Diabetes	1/5	4/6	0.24
Metabolic syndrome	5/5	6/6	1.00
Antihypertensive use	5/5	6/6	1.00
Statin use	4/5	3/6	0.55
estimated GFR (MDRD) (ml/min/1.73m²)	43 (20-54)	34 (26-39)	0.72
GFR (ml/min)	105 (35)	100 (36)	0.83
BMI (kg/m²)	40.3 (37.3-43.5)	37.4 (35.8-40.0)	0.14
Systolic blood pressure (mmHg)	118 (116-142)	135 (117-144)	0.47
Diastolic blood pressure (mmHg)	80 (72-88)	81 (65-92)	0.86
Total cholesterol to HDL cholesterol ratio	4.9 (3.5-5.7)	4.1 (3.2-4.6)	0.27
Triglycerides (mmol/L)	1.5 (1.3-2.2)	1.2 (0.9-1.7)	0.31
Weight (kg)	109.8 (8.0)	108.9 (13.2)	0.89
Fat mass (kg)	51.9 (5.5)	46.7 (6.5)	0.22
Waist (cm)	125.7 (8.6)	121.3 (8.8)	0.42
Waist to hip ratio	0.91 (0.91-1.00)	1.01 (0.94-1.02)	1.00
Adiponectin (mg/L)	11.6 (10.4-19.2)	10.2 (9.2-15.9)	0.52
Leptin (µg/L) **mean (SD)**	34.7 (25.4-257.7) 120.2 (178.5)	86.8 (31.9-104.7) 75.8 (41.2)	0.36
IL-6 (ng/L) **mean (SD)**	1.9 (0.7-11.0) 5.0 (7.2)	2.1 (1.1-4.3) 2.5 (1.8)	0.86
TNF-α (ng/L) **mean (SD)**	0.7 (0.5-4.6) 2.2 (3.0)	1.0 (0.8-1.3) 1.1 (0.3)	0.71
hs-CRP (mg/L) **mean (SD)**	5.0 (1.2-17.8) 8.6 (8.6)	4.1 (2.9-17.1) 9.1 (10.2)	1.00
Fetuin-A (mg/L) **mean (SD)**	665.4 (590.0-696.7) 647.8 (55.6)	662.9 (546.5-709.9) 623.1 (88.5)	0.92
HOMA-IR	3.0 (1.8-8.5)	7.8 (4.5-25.6)	0.20

data expressed as mean, (standard deviation, SD), or median (inter-quartile range) unless otherwise stated; BMI, body mass index; GFR, glomerular filtration rate, hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; MDRD, 4-variable Modification of Diet in Renal Disease study equation; TNF-α, tumour necrosis factor alpha; *p values obtained with independent samples Mann-Whitney U test, Student t-test, or Fisher's exact test as appropriate

There was wide variation in the leptin values, with one outlier value of > 400 µg/L in the BMC group. All other leptin values at baseline ranged between 17-130 µg/L.

There was wide variation in hs-CRP at baseline, with values ranging from 0.8 to 28.1 mg/L. 6 patients had an elevated hs-CRP > 5mg/L, and 5 patients had normal hs-CRP levels at the beginning of the study. IL-6 and TNF-α values were lower than those previously reported for obese patients with stages 3-4 CKD and were similar to levels reported in healthy subjects (Teplan, Vyhnanek et al. 2010; Spoto, Leonardis et al. 2012).

GFR values were consistently higher than the eGFR values in both groups at baseline, with eGFR under predicting GFR, on average, by 65.9 ml/min at baseline ($p < 0.001$). Patients classified as stage 3 CKD by eGFR at baseline showed a greater bias in the underestimation of GFR by eGFR than patients with eGFR-determined stage 4 CKD (Figure 17). There were no associations between eGFR and GFR values at baseline (Spearman $r = 0.54$, $p = 0.11$), or 12 months (Spearman $r = -0.05$, $p = 0.89$), but there was a significant association between eGFR and GFR at 6 months (Spearman $r = 0.80$, $p = 0.01$).

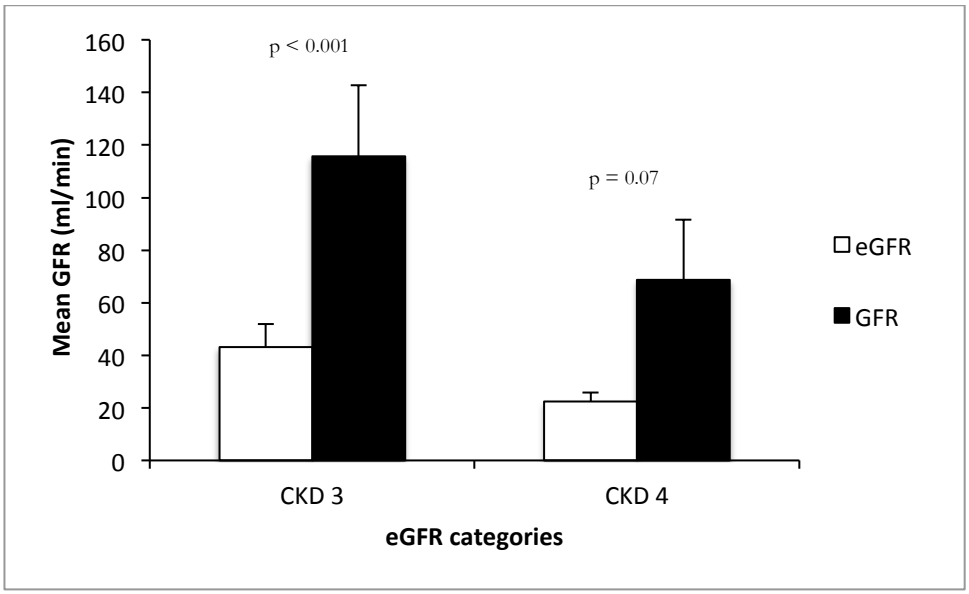


Figure 17: Bias between eGFR and GFR in CKD stages 3-4 obese patients at baseline. The error bars represent one standard deviation.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate using the 4-variable modification of diet in renal disease study equation; GFR, glomerular filtration rate measured using the iohexol clearance method

Compliance with interventions

All 8 patients allocated to the BMC group were invited to attend our Renal WMP. One patient withdrew from the study prior to baseline data collection. 6 of the remaining 7 patients commenced the programme, and 4 completed the full 12-month programme with attendance at 90% of sessions. 1 patient withdrew from the study after 5 months, and 1 patient attended 67% of the sessions and completed the study. 1 patient completed the study data collection visits, but did not attend the WMP.

Half of the patients attending the WMP were unable to obtain orlistat for the full duration of the study due to an international problem with production of the drug, which occurred from late 2011 and continued until the end of the study. All patients attending the WMP were compliant with both the dietary and physical activity components of the programme up to 6 months. Physical activity decreased after 6 months in most patients due to injury, change of environment and feeling unsafe to exercise outdoors, or reported low mood.

8 patients were randomised to the SG group. 2 patients refused the surgical intervention after randomisation and withdrew from the study. Five patients had SG surgery during the study and 1 patient was still on the waiting list for this procedure at the point at which baseline data collection was finalised, and could not be included in the study.

Compliance with post-weight loss surgery dietary recommendations was generally good, with 5 out of 6 patients following a high protein liquid diet in the initial post-operative period. One patient misunderstood the instructions and continued with clear fluids only for 4 weeks. All 6 patients in the SG group progressed to soft foods and then normal foods with considerably reduced portions, and continued to eat smaller meals portions up to 12 months. All patients were encouraged to increase their physical activity level, and many reported being more active, although this was not measured objectively during the study.

All patients were well nourished at baseline and remained well nourished throughout the study with Subjective Global Assessment ratings of A – well nourished (Detsky, Mclaughlin et al. 1987), achieved by all patients at 3-monthly intervals throughout the study.

Kidney function

Figure 18 illustrates the changes in both measured and estimated kidney function over 12 months in both treatment groups displayed as boxplots (median, interquartile range). The SG group show a decrease in hyperfiltration after 12 months, which is not evident in the

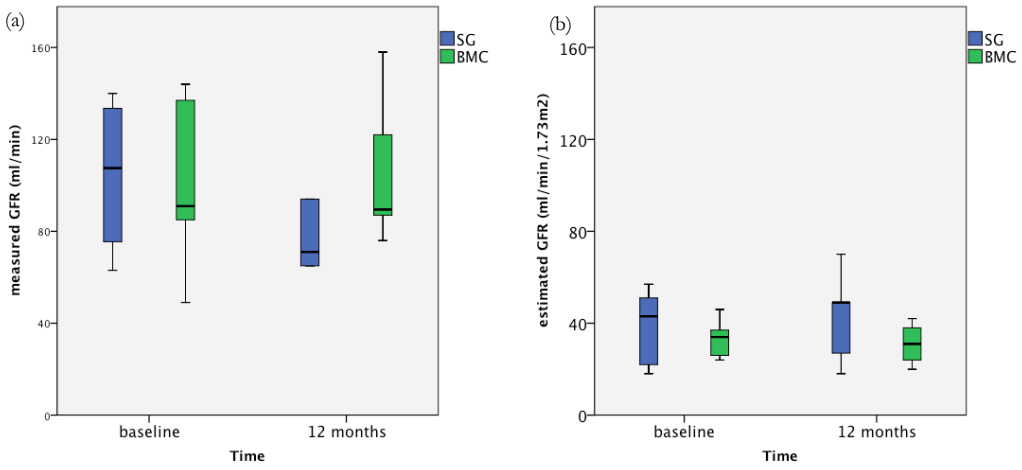


Figure 18: Boxplots of (a) measured GFR and (b) estimated GFR in obese patients with CKD randomised to either laparoscopic sleeve gastrectomy (SG) or best medical care (BMC)
eGFR, estimated glomerular filtration rate using the 4-variable Modification of Diet in Renal Disease study equation; GFR, glomerular filtration rate measured using the iohexol clearance method

BMC group. Changes in eGFR do not appear to predict changes in GFR in obese patients after weight loss surgery.

As the eGFR classified CKD stage 3 group demonstrated hyperfiltration at baseline, changes in GFR over 12 months were also examined separately by baseline CKD stage (Figure 19). In patients classified as CKD stage 3, there was a trend towards a reduction in hyperfiltration over time in the SG group, but not in the BMC group. Patients with stage 4 CKD displayed a trend towards a slight improvement in GFR over 12 months in the SG group, with little change in the BMC group.

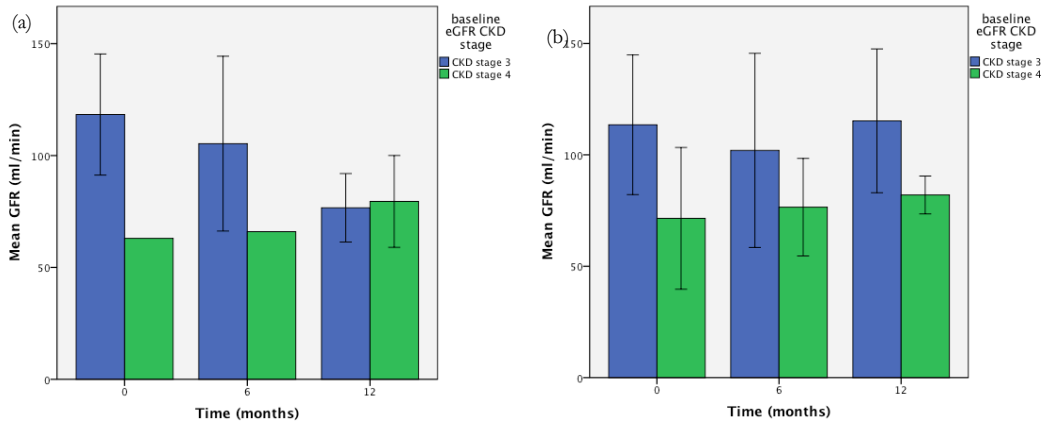


Figure 19: Changes in GFR over time by eGFR classified CKD stage in obese patients with CKD after (a) sleeve gastrectomy, or (b) best medical care

Error bars represent one standard deviation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate using the 4-variable modification of diet in renal disease study equation; GFR, glomerular filtration rate measured using the iohexol clearance method

Improvements in or resolution of co-morbidities

Table 22 and Table 23 outline the changes in co-morbidities related to obesity and CKD over the course of the study. There was no change in diabetes prevalence throughout the study. The 1 patient on insulin therapy in the SG group decreased their insulin dose by 59%, and the 4 patients requiring insulin in the BMC group decreased their median insulin dose by 7% over 12 months.

Table 22: Changes in diabetes, insulin resistance and hypertension in obese patients with stages 3-4 chronic kidney disease after laparoscopic sleeve gastrectomy or best medical care

Co-morbidity		Diabetes		Median Insulin Dose (units)	Insulin resistance (HOMA-IR >2)		Hypertension		Median Anti-hypertensive Score
Group		Y	N		Y	N	Y	N	
SG	baseline	1	4	102	4	1	5	0	86
	6 months	1	4	55	0	5	5	0	62
	12 months	1	4	43	1	4	5	0	62
BMC	baseline	4	2	60	5	1	6	0	74
	6 months	4	2	52	5	1	6	0	74
	12 months	4	2	56	4	2	6	0	63

BMC, best medical care; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance, ≥ 2.0 indicates insulin resistance; SG, sleeve gastrectomy

In patients who were insulin resistant at baseline, insulin resistance resolved in 3 out of 4 patients in the SG group, and in 1 of 5 patients in the BMC group. Whilst all patients in the study remained hypertensive throughout, antihypertensive medication use, quantified using the Antihypertensive Score method (Meier, Nitschke et al. 2006), decreased by 28% in the SG group and by 15% in the BMC group ($p > 0.05$ between groups at 12 months).

Table 23: Changes in proteinuria, blood lipids and metabolic syndrome status in obese patients with stages 3-4 chronic kidney disease after laparoscopic sleeve gastrectomy or best medical care

Co-morbidity		Albuminuria		Proteinuria		Total cholesterol < 4 mmol/L		LDL cholesterol < 2 mmol/L		Metabolic syndrome	
Group		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
SG	baseline	3	2	2	3	0	5	0	5	5	0
	6 months	1	4	0	5	0	5	0	5	2	3
	12 months	2	3	1	4	1	4	2	3	3	2
BMC	baseline	3	3	1	5	2	4	2	4	6	0
	6 months	2	4	2	4	3	3	3	3	6	0
	12 months	3	3	2	4	3	3	3	3	6	0

Albuminuria albumin:creatinine ratio >30 mg/mmol if no diabetes, or >2.5 mg/mmol in women or >3.5 mg/mmol in men with diabetes; BMC, best medical care; Proteinuria protein:creatinine ratio >50 mg/mmol; SG, sleeve gastrectomy

At 6 months, albuminuria fell below the clinically significant threshold in 2 of the 3 patients in the SG group with albuminuria at baseline. However, by 12 months, 1 of these patients had again developed albuminuria. 2 of 5 patients in the SG group were proteinuric at baseline, which resolved in both patients by 6 months, but returned at 9 months in 1 patient. There were no improvements in albuminuria or proteinuria in the BMC group.

All 5 patients in the SG group had total and LDL cholesterol levels above the Renal Association guideline of < 4 mmol/L and < 2 mmol/L (Renal Association 2007), respectively, at baseline. The total cholesterol target was reached by 1 of the 5 patients, and the LDL cholesterol target was reached by 2 of the 5 patients, at 12 months. In the

BMC group, 2 of the 6 patients met both guideline recommendations at baseline, and 3 of the 6 patients met the recommendations for total and LDL cholesterol after 12 months.

Metabolic syndrome resolved in 3 of the 5 patients in the SG group at 6 months, but remained resolved in only 2 patients by 12 months. There was no resolution of metabolic syndrome in the BMC group.

Quality of Life measures

There was a decrease in anxiety and depression scores from baseline to 12 months in the SG group, but not in the BMC group (Table 24).

Table 24: Hospital Anxiety and Depression Scale (HADS) measures in obese patients with stages 3-4 CKD after sleeve gastrectomy or best medical care

Parameter	Treatment Group	Baseline	6 months	12 months	12 month difference
HADS Anxiety Scale	SG	7 (2, 12)	5 (0, 10)	2 (0, 7)	-4 (-7 to -1)
	BMC	7 (3, 12)	6 (2, 11)	7 (3, 13)	
HADS Depression Scale	SG	7 (1, 13)	2 (0, 6)	1 (0, 6)	-5 (-8 to -2)
	BMC	7 (2, 12)	5 (2, 8)	7 (2, 11)	

Values are mean (95% confidence interval); mean difference for between group analysis of variance corrected for baseline values; BMC, best medical care; SG, sleeve gastrectomy

At 12 months, HADS scores were significantly reduced in the SG group, compared to the BMC group, after adjustment for baseline scores. Changes in SF-36 quality of life domain scores are displayed in Figure 20. SF-36 physical domain quality of life scores improved in the SG group, and declined in the BMC group over 12 months. At 12 months, the SG group had a significantly higher SF-36 physical domain score compared to the BMC group, after correction for baseline values (mean difference 20; 95% CI 4 to 35). There was no difference in SF-36 mental domain quality of life scores between groups at 12 months, after correction for baseline values (mean difference 8; 95% CI -7 to 24).

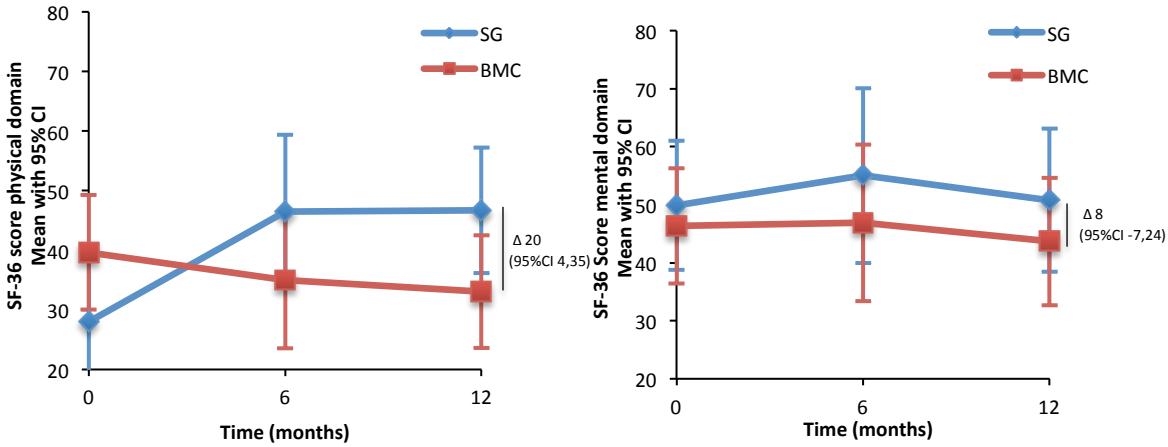


Figure 20: SF-36 physical and mental health domain summary scores in obese patients with stages 3-4 CKD after sleeve gastrectomy or best medical care

Weight loss and body composition changes

After 12 months, median % weight loss was 27.6% in the SG group and 4% in the BMC group. Median % excess BMI loss was 91.5% in the SG group and 11.1% in the BMC group. For comparison with previous studies of weight loss surgery, median excess weight loss was 72.6% in the SG group and 7.3% in the BMC group. Parameters of weight loss and changes in BMI are presented in Table 25.

Table 25: BMI and weight loss measures in obese patients with stages 3-4 chronic kidney disease after laparoscopic sleeve gastrectomy or best medical care

Parameter	Group	Baseline	3 months	6 months	9 months	12 months	12 month difference (95% CI)[c]
BMI (kg/m²)[a]	SG	40.3 (37.3-43.5)	32.5 (30.9 - 36.8)	29.0 (27.3 - 34.3)	26.8 (26.4 - 33.4)	26.3 (25.7 - 32.3)	8.1 (3.6, 13.7)
	BMC	37.4 (35.8-40.0)	36.7 (32.4 - 38.7)	36.5 (30.9 - 37.8)	36.6 (32.0 - 38.3)	36.5 (33.5 -39.4)	
% weight loss[b]	SG	-	-17.0 (3.9)	-24.8 (5.5)	-27.9 (6.1)	-29.8 (4.9)	-26.6 (-32.2, -21.1)
	BMC	-	-5.12 (3.8)	-7.4 (5.7)	-5.0 (4.2)	-3.1 (2.6)	
% excess BMI loss[b]	SG	-	-46.1 (12.8)	-67.2 (17.8)	-75.6 (15.6)	-80.8 (9.6)	-79.8 (-95.5, -64.2)
	BMC	-	-10.7 (13.0)	-15.4 (19.6)	-9.8 (14.5)	-8.4 (18.4)	

for definitions of weight loss see Chapter 3; [a]data are presented as median (inter-quartile range); [b]data are presented as mean (95% confidence interval); [c]Hodges-Lehman median difference (95% confidence interval) between groups at 12 months or mean difference (95% confidence interval) between groups at 12 months corrected for baseline values; BMC, best medical care; CI, confidence interval for difference between groups at 12 months; SG, sleeve gastrectomy

The difference in BMI between groups after 12 months was 8.1 kg/m^2 (95% CI 3.6 to 13.7 kg/m^2). Patients in the SG group decreased their weight progressively throughout the study, whilst weight loss was maximal after 6 months in the BMC group, with some weight regain evident from 6 to 12 months.

Changes in body weight and body composition are illustrated in Figure 21. There was statistically significant mean weight loss between baseline and 12 months within both the BMC group ($p = 0.04$) and in the SG group ($p < 0.001$). The SG group also demonstrated statistically significant reductions in waist circumference ($p = 0.002$), fat mass ($p = 0.004$) and lean body mass ($p = 0.008$) after 12 months. Changes in waist circumference, fat mass and lean body mass loss were not statistically significant in the BMC group between baseline and 1 year.

Greater reductions in body weight, waist circumference, and body fat mass were evident in the SG group, when compared to the BMC group after 12 months (Figure 21). Mean differences (95% CI) for body weight, waist circumference, fat mass and lean mass, corrected for baseline values, were -29 (-36.4 to -22.3) kg, -29.1 (-40.6 to -17.6) cm, -24.1 (-32.5 to -15.7) kg, and -5.9 (-8.5 to -3.3) kg, respectively. Mean waist-to-hip ratio decreased from 0.95 to 0.87 after 12 months in the SG group and from 0.99 to 0.96 in the BMC group. After 12 months the mean difference in waist to hip ratio between groups was -0.09 (-0.18 to -0.008).

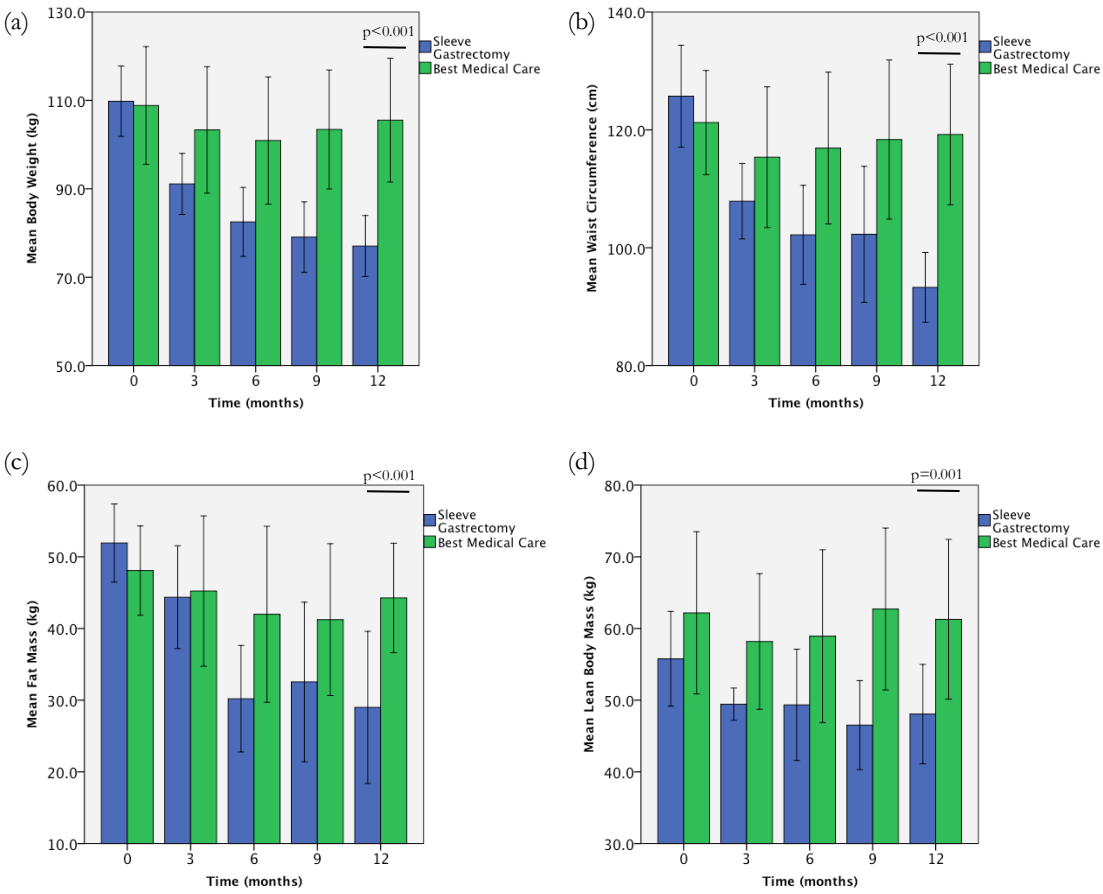


Figure 21: Mean (a) body weight; (b) waist circumference; (c) body fat mass; and (d) lean body mass in obese patients with chronic kidney disease stages 3-4 after sleeve gastrectomy or best medical care

Error bars represent ±1 standard deviation; p values represent between group differences at 12 months corrected for baseline values

While it is clear that the SG group lost more weight and fat mass than the BMC group, examination of the changes in body fat and lean body mass highlight some differences between the groups over the course of the study. The SG group showed a rapid decrease in fat mass over the first 6 months, and the BMC group lost fat mass more gradually over the same time period. Body fat mass remained quite stable in both groups between 6 and 12 months. The weight gain evident between 6 and 12 months in the BMC group may be partially attributed to an increase in lean body mass over this period, which was not seen in the SG group.

Adipokines, insulin resistance, markers of inflammation, and fetuin-A

Table 26 displays the changes in adipokines, insulin resistance, inflammatory markers, and fetuin-A, all considered to be novel indicators of cardiovascular disease risk, over 12 months after patients were randomly assigned to either SG or BMC. It should be noted that this pilot study was not powered to detect changes in these markers and the analyses were performed for exploratory purposes only.

Table 26: Changes in novel cardiovascular disease risk factors over 12 months in obese patients with stages 3-4 chronic kidney disease after sleeve gastrectomy or best medical care

Parameter		Baseline	3 months	6 months	9 months	12 months	12 month difference[c]
Leptin (µg/L)[a]	SG	120.2 (178.5)	60.5 (67.5)	40.6 (27.9)	47.7 (34.8)	54.4 (73.2)	-11.5 (-108.3, 85.3)
	BMC	75.8 (41.2)	86.4 (61.3)	143.3 (93.1)	69.8 (65.1)	68.5 (56.6)	
Adiponectin (mg/L)[b]	SG	11.6 (10.4-19.2)	8.6 (8.4-18.1)	11.6 (9.2-20.8)	17.7 (14.3-21.0)	14.7 (13.7-21.2)	6.1 (1.0, 19.8)
	BMC	10.2 (9.2-15.9)	10.7 (5.9-12.7)	11.0 (9.3-11.5)	10.3 (8.9-11.8)	9.0 (7.8-12.4)	
HOMA-IR[b]	SG	3.0 (2.4-5.6)	2.3 (1.6-2.2)	1.1 (1.0-1.1)	0.93 (0.6-1.2)	0.9 (0.8-1.0)	-7.7 (-28.8, -0.5)
	BMC	7.8 (5.5-21.3)	7.2 (3.3-15.0)	7.6 (2.3-20.5)	7.1 (2.2-10.2)	9.4 (1.9-16.4)	
hs-CRP (mg/L)[a]	SG	8.6 (8.6)	3.4 (3.0)	2.6 (3.4)	2.5 (2.8)	1.7 (2.4)	-2.4 (-6.3, 1.6)
	BMC	9.1 (10.2)	2.6 (1.9)	4.0 (2.6)	3.6 (2.7)	4.1 (3.0)	
IL-6 (ng/L)[a]	SG	5.0 (7.2)	3.1 (4.6)	2.0 (1.7)	13.5 (23.8)	2.3 (1.8)	-15.8 (-58.5, 26.9)
	BMC	2.5 (1.5)	1.4 (0.7)	3.7 (4.8)	1.4 (0.9)	23.6 (40.7)	
TNF-α (ng/L)[a]	SG	2.2 (3.0)	0.8 (0.5)	1.1 (0.7)	6.8 (5.8)	2.4 (1.5)	-0.5 (-2.1, 1.2)
	BMC	1.1 (0.3)	1.0 (0.4)	0.9 (0.6)	1.6 (1.1)	3.4 (1.2)*	
Fetuin-A (mg/L)[a]	SG	648 (56)	539 (136)	515 (136)	503 (142)	502 (141)	-19 (-186, 149)
	BMC	623 (88)	597 (141)	533 (110)	466 (75)	501 (113)*	

* $p < 0.05$ within group difference from baseline; [a] data are presented as mean (SD); [b] data are presented as median (inter-quartile range); [c] mean differences (95% confidence interval) between groups at 12 months corrected for baseline values or Hodges-Lehman median difference (95% confidence interval) between groups at 12 months; BMC, best medical care group; HOMA-IR, homeostasis method of assessment – insulin resistance; hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; SG, sleeve gastrectomy group; TNF-α, tumour necrosis factor - alpha

Leptin levels decreased in the SG group yet in the BMC group leptin levels rose up to 6 months, then returned to baseline by 12 months. Despite the decrease in serum leptin

level in the SG group at 12 months, this was not significantly different to the BMC group due to the wide variation in serum leptin levels throughout the study.

Median serum adiponectin increased significantly in the SG group, compared to BMC at 12 months. HOMA-IR, a measure of insulin resistance, decreased in the SG group, compared to BMC at 12 months, reflecting the increase in adiponectin. Insulin resistance was higher in the BMC group, more patients were requiring insulin therapy for blood glucose control in this group at baseline. The reduction in HOMA-IR over 12 months was adequate to reduce insulin resistance to a subclinical level in most patients in the SG group, but not in the BMC group.

The reductions in hs-CRP evident in the both the SG group and the BMC group brought the hs-CRP level below the conventional threshold level for normal hs-CRP in both groups by 12 months, indicating that the reduction in hs-CRP may be clinically relevant across the whole study population. There was a decrease in Fetuin-A within both groups from baseline to 12 months, which mirrored the reductions in HOMA-IR and hs-CRP.

The large variation in IL-6 results may be explained by two spurious individual values, reflected by the large changes in the standard deviations for the SG group at 9 months and for the BMC group at 12 months, compared to the confidence intervals for the other time points. Notwithstanding these anomalies, there may be up to a 50% decrease in IL-6 in both groups 12 months after commencing either weight loss surgery or the weight management programme. TNF-α decreased between baseline and 6 months in the SG group, but remained stable in the BMC group. At 9 months, TNF-α increased in the SG group, then returned to baseline by 12 months. TNF-α increased in the BMC group between 6 and 12 months ($p = 0.01$).

Associations between changes in weight loss and exploratory variables

Spearman rank correlations were performed to determine if changes in body weight and fat mass were related to changes in quality of life, and metabolic and haemodynamic variables. Weight loss was associated with an improvement in the SF-36 physical domain score ($r = -0.88$, $p = 0.002$), a reduction in the HADS depression score ($r = 0.65$, $p = 0.06$), and an increase in adiponectin ($r = -0.75$ $p = 0.008$), in the entire study group after 12 months. In the SG group only, weight loss was associated with a decrease in leptin ($r = 0.9$ $p = 0.04$), and the change in leptin was inversely associated with the change in adiponectin ($r = - 0.9$ $p = 0.04$) after 12 months. In the BMC group only, weight loss, and fat mass loss were both associated with a reduction in triglycerides ($r = 0.89$, $p = 0.04$; and $r = 0.95$, $p = 0.05$, respectively).

In all patients, a reduction in fat mass was related to an increase in adiponectin ($r = -0.77$, $p = 0.02$), and a decrease in waist circumference ($r = 0.9$, $p = 0.001$), indicating that abdominal obesity was reduced with both weight loss interventions. Yet, neither changes in fat mass, insulin resistance, leptin or adiponectin were associated with changes in markers of inflammation after 12 months. However, in the BMC group only, associations were observed between increased in leptin and hs-CRP ($r = 0.89$, $p = 0.02$), and between increased TNF-α and HOMA-IR ($r = 0.94$, $p = 0.005$), after 12 months.

Proteinuria was positively associated with adiponectin ($r = 0.74$, $p = 0.09$) and inversely associated with hs-CRP ($p = -0.73$, $p = 0.01$), at baseline. A change in proteinuria was not related to a change in adiponectin in the entire study group, or in either of the intervention groups after 12 months. However, a change in proteinuria was directly associated with a change in HOMA-IR ($r = 0.66$, $p = 0.04$), in both the entire study group, and in the BMC group ($r = 0.9$, $p = 0.04$), after 12 months, despite no relationship between these variables at baseline. In the BMC group, changes in HOMA-IR were positively correlated with

changes in adiponectin (r = 0.9 p = 0.04) at 12 months. In the SG group, the change in proteinuria was related to the 12-month changes in both systolic and diastolic blood pressure (r = 0.9 p = 0.04 for both). There was no relationship between changes in proteinuria and either fat mass or weight loss. Fetuin-A is known to increase with obesity, and fetuin-A levels decreased in both groups over 12 months, although this was not associated with weight loss or change in fat mass in this study.

Safety and adverse events

Orlistat, when available for use in this study, was well tolerated in the BMC group. Episodes of diarrhoea – a common side effect of a moderate to high fat intake concomitant with orlistat - occurred during the first 2 months of orlistat use only, whilst the patients adapted to a low fat diet. There was no incidence of acute kidney injury or acute oxalate nephropathy, both of which have been previously reported with orlistat use in patients with CKD (Singh, Sarkar et al. 2007; Weir, Beyea et al. 2011).

In the SG group, the median length of perioperative stay was 5 days, and ranged from 2 to 8 days. There were 2 post-operative re-admissions to hospital. Two weeks post-operatively, a patient was admitted with acute kidney injury secondary to dehydration. The patient was treated with intravenous fluids and discharged after 2 days, and serum creatinine returned to baseline within 3 months. The second patient was admitted 4 weeks post-operatively with dehydration, secondary to nausea and vomiting. No surgical reason was found for the nausea and vomiting, and a liquid and puree diet was encouraged. Prior to admission this patient experienced a decline in her mobility and her discharge was delayed, as she required rehabilitation therapy.

Two patients in the SG group reported epigastric pain, occurring at 1 and 3 months post-operatively. One patient in the SG group reported constipation at 9 months. One patient in the BMC group reported foot and lower leg pain at 6 months and this was investigated for possible deep vein thrombosis, which was not found. This patient was subsequently diagnosed with neuropathic arthropathy of the ankle (Charcot Foot), which may have been exacerbated by his increased physical activity level during the study.

All patients were well nourished using the Subjective Global Assessment (Detsky, Mclaughlin et al. 1987) when commencing the study. The patient admitted to hospital 4 weeks post-sleeve gastrectomy, had mild to moderate malnutrition based on the Subjective Global Assessment of nutritional status at the time of hospitalisation. Nutritional status had returned to baseline by 3 months post-operatively. All other patients remained well nourished throughout the study.

There was no cardiovascular morbidity and no mortality in this study.

Discussion

This study is the first randomised controlled study of sleeve gastrectomy compared to best medical care, including a structured lifestyle modification programme, in obese patients with stages 3-4 CKD. A pilot study design was chosen to explore the primary and secondary outcomes, and also to examine the feasibility of the study design and examine the utility of the outcome measures selected.

Weight loss

Significant weight loss was achieved after 12 months in both the SG and BMC groups, and weight loss was associated with increases in serum adiponectin and the SF-36 physical domain quality of life score, and a reduction in HADS depression score. Reductions in fat mass were associated with a decrease in waist circumference and an increase in serum adiponectin after 12 months. In the SG group, weight loss was associated with a decrease in serum leptin, and leptin was inversely related to adiponectin, and changes in proteinuria were associated with changes in systolic and diastolic BP.

Weight loss in the present study compares favourably with the reported 56.1% excess weight loss 12 months after sleeve gastrectomy, in a 2012 meta-analysis of 123 studies published between 2003 and 2010 (Fischer, Hildebrandt et al. 2012). The greater excess weight loss achieved in the present study is likely to be attributable to the lower baseline BMI of the group, as an equivalent amount of absolute weight change equates to a greater excess weight loss when starting BMI is lower. Absolute percentage weight loss after 12 months in the present study was similar to findings reported in a non-randomised study of an otherwise similar design, for both weight loss surgery and for a lifestyle intervention conducted in a hospital outpatient clinic setting (Martins, Strømmen et al. 2011).

Kidney function

As far as could be determined there are no previous studies examining changes in measured kidney function with weight loss in obese patients with CKD. The present study hypothesised that kidney function would improve with weight loss, and this was apparent in the SG group, with trends towards a reduction in hyperfiltration, which was not evident in the BMC group.

Previous studies examining changes in estimated kidney function in obese patients with CKD after weight loss surgery have demonstrated reductions in hyperfiltration (Navarro-Diaz, Serra et al. 2006) and improvements in eGFR in patients with CKD stage 3 (Navaneethan and Yehnert 2009). However, as there was no association between eGFR and GFR in the present study, the effect of weight loss on eGFR in obese patients with CKD should be interpreted cautiously.

Although it has been reported that eGFR underestimates GFR in the obese (Delanaye, Radermecker et al. 2005), the degree of bias in the eGFR measurement in the present study was unexpected. A similar level of bias in eGFR was recently reported in overweight and obese patients with diabetic nephropathy, using the EDTA plasma clearance method of GFR measurement; eGFR under-predicted measured GFR with a progressively increasing bias with each stage of CKD through stages 1-4 (Nair, Mishra et al. 2011), although in the present study, the bias was greater in CKD stage 3 than stage 4.

Iohexol clearance measured GFR was also recently reported for the first time in obese subjects without CKD (Friedman, Strother et al. 2010). The MDRD study equation eGFR slightly over-predicted measured kidney function in obese subjects, and was associated with body weight and lean body mass only. Serum creatinine was inversely related to fat mass, but was not associated with lean body mass (Friedman, Strother et al. 2010). This reported lack of association between lean body mass and serum creatinine in obese subjects might, at least in part, explain the poor prediction of GFR by estimation equations based on serum creatinine in obese patients with CKD. Other reasons for the lack of association between eGFR, using the MDRD study prediction equation, and measured GFR include the under-representation of obese patients in the MDRD study sample, and the use of normalised body surface area, which is known to under-represent body surface area in

obesity (Levey, Bosch et al. 1999; Levey, Greene et al. 2000; Levey, Stevens et al. 2009; Friedman, Strother et al. 2010).

The degree of hyperfiltration evident in the eGFR classified stage 3 CKD patients was somewhat unexpected, and brings into question the use of eGFR classifications of CKD stage for obese patients. However, the clinical management would be largely unchanged, with the therapeutic aims to reduce blood pressure, optimise blood glucose control and blood lipids, reduce proteinuria, and achieve and maintain a healthy weight remaining paramount. The smaller change in kidney function with weight loss in patients with stage 4 CKD may be attributable to more advanced CKD in which the kidney damage already incurred may have been less reversible with weight loss (Palatini, Saladini et al. 2013).

As the change in kidney function may have differed by baseline CKD stage, and the sample size is small, it is difficult to examine the effect of the change in kidney function on other variables. The relationship between change in kidney function and change in adiponectin, would have been pertinent to examine. The associations between adiponectin and reduction in weight and fat mass in the present study may have mediated the change in kidney function evident with weight loss. Adiponectin receptors are present in renal tubular cells and are likely to play a role in the inhibition of angiotensin II-induced oxidative stress and fibronectin expression, which may impact upon the progression of CKD by limiting oxidative stress, inflammation and fibrosis (Fang, Liu et al. 2013). Further studies, in which adiponectin levels are manipulated to mimic adiponectin deficiency in obesity and increasing adiponectin with weight loss, may help to elucidate some of the mechanisms of the effect of weight loss on kidney function.

Novel cardiovascular risk factors

It may be useful to put the study group into context by comparing baseline levels of, and changes in, adipokines with those in obese patients without CKD. Patients in the present study had higher baseline leptin and adiponectin levels than obese patients without CKD undergoing weight loss surgery, who underwent either sleeve gastrectomy or gastric bypass, and demonstrated a relatively lower reduction in leptin and increase in adiponectin, which was remarkably consistent between the other two studies (Serra, Granada et al. 2006; Woelnerhanssen, Peterli et al. 2011). These comparisons indicate that there is likely to be an additive effect of obesity and CKD on serum levels of adipokines in obese patients with CKD, and that weight loss results in favourable improvements in adipokines. Both leptin and adiponectin remained elevated after weight loss, when compared to levels 12 months post weight loss surgery in obese patients without CKD (Serra, Granada et al. 2006; Woelnerhanssen, Peterli et al. 2011). This result may reflect the impact of CKD upon serum leptin and adiponectin levels, masking the full physiological impact of weight loss in obesity. This phenomenon may go some way to explaining the disparate findings of studies demonstrating that both high and low levels of adiponectin are related to poorer outcomes in patients with CKD (Zoccali, Mallamaci et al. 2002; Iwashima, Horio et al. 2006; Menon, Li et al. 2006; Iglesias and Diez 2010), as there may be an anti-inflammatory, anti-atherosclerotic mechanism driving a rise in adiponectin, developed as a counter-regulatory response to the hyperleptinaemic, uraemic, pro-inflammatory environment of CKD.

Despite significantly greater weight loss, and reductions in waist circumference and body fat mass in the SG group compared to the BMC group after 12 months, there was no remission in diabetes or reduction in hypertension, and little change in blood lipids and metabolic syndrome in the SG group. This finding supports a previous randomised trial of

gastric banding weight loss surgery, compared to lifestyle weight loss treatment in obese adolescents, which demonstrated no changes in blood lipids or blood pressure after weight loss surgery despite substantial weight loss (O'Brien, Sawyer et al. 2010), yet contrasts to previous studies of weight loss surgery in obese patients without CKD (Hofso, Nordstrand et al. 2010; Martins, Strømmen et al. 2011). In the SG group, the change in proteinuria was related to the 12-month changes in both systolic and diastolic BP ($r = 0.9$, $p = 0.04$ for both), and this may have been influenced by an increase in BP and proteinuria in one patient, who ceased taking anytihypertensive medication 3-6 months post SG, given the small sample size in this study, and countered any effect of weight loss on improvements in proteinuria or BP overall.

In the BMC group, weight loss was associated with a reduction in triglycerides, and changes in HOMA-IR were positively associated with changes in adiponectin after 12 months. Weight loss in the BMC group was achieved with a combination of dietary modifications to reduce total fat and energy intake, an increase in physical activity, and the lipase inhibitor orlistat. Previous studies on lifestyle-based weight loss interventions have used mainly dietary restrictions in obese patients with CKD, and have largely been focused on patients with proteinuria (Navaneethan, Yehnert et al. 2009), without stating the eGFR range, so differences in the level of kidney function may impact upon the results. Most studies report a reduction in proteinuria with lifestyle-based weight loss interventions, yet there was little proteinuria at baseline in the present study. There was no change in triglycerides with weight loss in a combined analysis of previous studies (Navaneethan, Yehnert et al. 2009), so the change evident in the present study may be attributable to the use of orlistat (Bougoulia, Triantos et al. 2006), rather than to physical activity (Fayh, Lopes et al. 2012). The weight loss achieved in the current study appeared insufficient to induce a change in adiponectin in the BMC group. Studies achieving >10% absolute weight loss

with lifestyle modifications report positive changes in adiponectin, triglycerides, IL-6, CRP, insulin resistance and leptin in obese women without CKD (Esposito, Pontillo et al. 2003; Bougoulia, Triantos et al. 2006).

There was no association found between weight loss and changes in markers of inflammation in the present study, which may be attributed to the relatively low level of IL-6 and hs-CRP in the study participants at baseline, compared to obese patients without CKD undergoing weight loss surgery or lifestyle weight loss treatment, and non-obese patients with CKD (Esposito, Pontillo et al. 2003; Bougoulia, Triantos et al. 2006; Illan-Gomez, Gonzalvez-Ortega et al. 2012; Spoto, Leonardis et al. 2012). Previous cross-sectional studies have demonstrated inflammation across patients with stages 2-5 CKD, with increases in serum IL-6 evident in the earlier stages of CKD and remaining elevated, and an eGFR dependent rise in serum TNF-α (Spoto, Leonardis et al. 2012). Studies differ in their findings for changes in TNF-α with weight loss, yet no change in TNF-α after weight loss surgery has been reported previously, and the authors postulated that adipose tissue TNF-α, may not directly influence serum levels of TNF-α (Illan-Gomez, Gonzalvez-Ortega et al. 2012). Indeed, measured adipose tissue mRNA levels of pro-inflammatory cytokines IL-6 and TNF-α do not correlate with serum levels, indicating that markers of inflammation evident in serum samples may be related to uraemia or macrophage concentration, rather than to adipocytes (Spoto, Leonardis et al. 2012). As inflammation is likely related to kidney function, it may be postulated that the lower than expected levels of inflammatory markers are perhaps due to the measured GFR being much higher than the eGFR in this study, and thus, the study participants are not directly comparable to non-obese patients with stages 3-4 CKD.

Proteinuria was positively associated with adiponectin at baseline, which has also been reported previously in CKD (Looker, Krakoff et al. 2004). This may reflect a counter-regulatory response to limit kidney damage, as adiponectin acts via the mitogen-activated protein kinase pathway to reduce oxidative stress, and may play a role in podocyte foot process fusion in an attempt to prevent further albuminuria or proteinuria (Liao, Sung et al. 2012). Podocyte hypertrophy has also been characterised in obesity-related glomerulopathy (Serra, Romero et al. 2008) and may occur as an adaptive response to an early increase in oxidative stress and microalbuminuria, in order to prevent further damage to the podocyte and maintain protein homeostasis by maintaining the integrity of the filtration barrier (Fornoni 2010). The change in proteinuria was not related to changes in adiponectin in either of the intervention groups after 12 months. In the entire study population, changes in proteinuria after 12 months were associated with changes in insulin resistance, measured by HOMA-IR, and changes in the pro-inflammatory cytokine TNF-α, a finding also reported previously in a study of weight loss in non-diabetic obese women with and without albuminuria (Gilardini, Zulian et al. 2010). Insulin resistance can be induced by TNF-α, and high levels of TNF-α inhibit insulin signalling and glucose uptake in humans (Liao, Sung et al. 2012). Fetuin-A may also induce insulin resistance and correlates with fat mass and truncal fat mass in CKD (Axelsson, Wang et al. 2008; Liao, Sung et al. 2012).

Serum fetuin-A decreased in both the groups after 12 months. Weight loss was not associated with a reduction in fetuin-A, proteinuria or insulin resistance in the present study. Fetuin-A is a known inhibitor of adiponectin mRNA in adipose tissue, so a fall in fetuin-A levels with weight loss would reduce the inhibition of adiponectin production in adipose tissue, which may then result in a rise in serum adiponectin, which was evident in the present study. The lack of association between weight loss and fetuin-A or between fetuin-A and adiponectin may be due to the study's small sample size, or an unaccounted

for metabolic effect of CKD. Recent evidence suggests that obesity and diabetes are co-variates in the relationship between fetuin-A and cardiovascular risk (or metabolic syndrome), which may provide an alternative explanation, although the small sample size in this present study precludes investigation of this effect (Ismail, Ragab et al. 2012; Jensen, Bartz et al. 2012).

Quality of Life

An improvement in the SF-36 physical domain score and a reduction in depression score were both associated with weight loss in the present study. These tools are robust measures of aspects of quality of life, and are easy to administer. Evidence of improvements in quality of life after sleeve gastrectomy in obese patients with CKD is a significant positive patient focused outcome. It has been demonstrated previously that SF-36 physical domain scores decrease progressively as CKD stages increase, and obesity also contributed to a further deterioration in the SF-36 physical health domain scores, compared to those of normal weight, regardless of CKD stage (Pagels, Soderkvist et al. 2012). Therefore, an improvement in SF-36 score in the present study related to weight loss likely reflects an improvement in the additional reduction in SF-36 score related to obesity in patients with CKD.

Safety of interventions for weight loss in stages 3-4 CKD

Whilst the sample size in the present study is too small to ascertain the safety of SG in obese patients with CKD, the experience of performing SG in this patient group may provide some learning points for future practice. 2 out of 5 patients in the SG group experienced dehydration requiring hospital readmission in the 30-day post operative period. Fluid, electrolyte or nutritional depletion occurs in 2% of patients undergoing sleeve gastrectomy (Hutter, Schirmer et al. 2011). The reduction in kidney function in this

patient group, with the encouraged reduction in fluid intake as CKD progresses to prevent and manage oedema, may increase the risk for dehydration post-operatively when total intake is volume restricted, yet fluid intake is encouraged, requiring a significant change in the pattern of fluid ingestion to maintain euvolaemia.

These results, taken together with those in the previous studies in Chapters 3 and 4, provide valuable early data to describe the experience of obese patients with CKD undergoing LSG weight loss surgery. CKD, in addition to obesity, may increase the risks of adverse events with LSG weight loss surgery, although the benefits must be balanced against the possible increase in risk in this population group. The benefits of weight loss in obese patients with CKD may include decreased insulin resistance, reduced insulin requirements, and decreased antihypertensive medication dose after 12 months. Furthermore, weight loss was associated with an improvement in quality of life scores in stages 3-4 CKD and an increased likelihood of qualifying for kidney transplantation in patients on haemodialysis, and these beneficial outcomes can be considered together with possible risks when making treatment decisions with individual patients.

Strength and limitations

Performing a pilot study was useful in several ways unrelated to the actual primary and secondary outcome measures. Conducting this pilot study identified significant problems in recruiting patients to a randomised controlled study of surgery compared to a non-surgical intervention. The recruitment process was very time-consuming and required many hours of not only screening databases and clinic lists, but then also talking to patients to provide enough information to them to enable them to make an informed decision about participating in the study. Waiting times for surgical appointments were long and this extended the recruitment time, as patients required a surgical assessment prior to being

able to provide informed consent. Capacity for elective surgery at the study centre was also compromised by a rise in acute medical care provision, including emergency surgery, which limited bed capacity and theatre time for elective surgery provision during the study period. Whilst the issue of capacity for delivering the required amount of surgical care in clinics and operating theatre lists was addressed prior to the study, and assurances were given that there would be capacity to accommodate the study patients, this was found not to be the case and was beyond the researchers' control. The rate of uptake into the study was only 9% of patients approached to participate. Additionally, 3 of the 16 patients consenting to the study declined the intervention they were allocated to, significantly reducing the numbers of patients actually commencing the study.

We now have over a decade of research on the effects of weight loss surgery, and an abundance of studies on medical and lifestyle adaptations for weight loss interventions for the management of obesity. However, there are still very few randomised trials exploring the differential effects of weight loss achieved by lifestyle or medical treatment, compared to weight loss surgery in obesity (O'Brien, Dixon et al. 2006; Dixon, O'Brien et al. 2008; O'Brien, Sawyer et al. 2010; Dixon, Schachter et al. 2012; Mingrone, Panunzi et al. 2012; Schauer, Kashyap et al. 2012). The majority of these studies have focused on the effects of the extent of weight loss achieved via the two approaches on outcomes related to the management of diabetes (O'Brien, Dixon et al. 2006; Dixon, O'Brien et al. 2008; O'Brien, Sawyer et al. 2010; Mingrone, Panunzi et al. 2012; Schauer, Kashyap et al. 2012), and one study examined the effects of weight loss surgery and low calorie diets on sleep apnoea events (Dixon, Schachter et al. 2012). The paucity of randomised intervention studies examining weight loss surgery and lifestyle management of obesity suggests that these trials may be difficult to conduct, and a number of factors may be contributory, such as expense, availability of expert clinicians to conduct the interventions, the difficulty in controlling the

environment sufficiently in a multi-modal intervention to maintain scientific rigour, or hesitancy on the part of prospective volunteers to participate in such a study.

The adoption of a randomised controlled study design and use of measured GFR as the primary outcome measure, were deemed strengths of the study design, prior to execution of the study. However, the very nature of the randomisation process itself, in such a design, with allocation by chance to surgery or lifestyle treatment, increased both the time taken for recruitment and the dropout rate. The dropout rate in the present study immediately after randomisation was 3/16 patients (18%), compared to 10% or less dropout at the same point in other randomised trials (Dixon, O'Brien et al. 2008; Dixon, Schachter et al. 2012). It was difficult to find patients actually in a state of equipoise themselves about treatment, so recruitment look longer than expected. Similarly, with only one person working on recruitment in 2 of the 3 centres, it was a slow methodical process to find patients meeting the study inclusion criteria. With such a small sample size and the pilot nature of the study, the results of the actual outcome measures themselves cannot always be interpreted, but the utility and practicality of the measures under study can be defined.

Use of measured GFR using the iohexol clearance method with fingertip blood sampling reduced the study visit time for patients, but may have impacted on the validity and reliability of the measure. The reliability is dependent upon the patients correctly recording the timing of their own blood sampling. Whilst they were provided with a battery operated device to make this process easier, the devices did not always work and the process is still reliant on the patient pressing the button at the time of blood sampling. This two-step process may have been difficult with many things to remember when carrying out this procedure in patients unfamiliar with the process. Patients demonstrated the technique

prior to leaving the clinic, however, there may have been errors made in this patient-performed data collection. The measurement of iohexol concentration from fingertip blood sampling onto blotting paper assumes that the volume of blood is a fixed amount across a given surface area (Mafham, Niculescu-Duvaz et al. 2007). As patients were instructed to completely fill the pre-marked circle on the blotting paper, a greater volume of blood may have been present if several drops of blood were used to fill the space, rather than the preferred single sample. Further validation of both the patient-provided sampling technique, and iohexol clearance GFR in obese patients with CKD itself, are required before further intervention studies exploring the effect of weight loss on kidney function in obese patients with CKD are undertaken.

An examination of the literature identified no previous studies using the iohexol clearance method for calculating GFR specifically in obese adults with known CKD, prior to the present study. It is now evident that a validation study may have been prudent, prior to embarking on a randomised controlled pilot study with iohexol GFR as the primary outcome measure. In a study published in 2010, notably after the study design for the present study was finalised and recruitment had begun, measurement of iohexol GFR using population pharmokinetics methodology was performed in 29 obese subjects without known CKD (Friedman, Strother et al. 2010). Iohexol clearance was found to follow a two-compartment model, rather than a one-compartment model, as used in the present study, although as there was a similar relationship between serum iohexol and total body iohexol reported in previous studies, it was concluded that there was no distribution of iohexol into body fat (Friedman, Strother et al. 2010). Lean body mass and total body weight, were the only factors impacting upon GFR, indicating that metabolic load is the major influence on GFR (Friedman, Strother et al. 2010). Additionally, both early (within 20 minutes) and later (2 to 4 hours) sampling times were required for optimal GFR

calculation; however the authors did acknowledge that a longer sampling period would be required in patients with CKD, due to slower iohexol clearance rates. Thus, the importance of the earlier sampling time in obese patients with CKD remains unknown (Friedman, Strother et al. 2010). The within-subject variability of GFR reported from up to 6 iohexol clearance measures was 8.8% (Friedman, Strother et al. 2010). This level of variability in obese patients may also impact upon the measurement of change in GFR, particularly over a 12-month time period, when expected changes may not be greater than this inherent variability.

The major limitation of this study is the sample size, and limitations of the applicability and external validity of the results that this brings. The study results are hypothesis-generating, and the data gathered would support the calculation of the required sample size to conduct a definitive study. Given the wide variation in the results for leptin and IL-6, adequately powered studies to address research questions pertaining to the effects of weight loss on these outcomes would need to be very large indeed. What should also be considered is the ability of any future study design to distinguish between the effect of weight loss, and any possible change in kidney function, on other outcomes. If weight loss is associated with an improvement in kidney function, the change in any secondary outcome may be associated with either effect, and it would be difficult to ascertain the pathways of these effects in a clinical study.

A realistic assessment of the likelihood of taking this research forward into a definitive study to address the principal research question in the present study, may indicate that it would be too onerous and expensive to conduct. Given that the number of patients requiring screening was in the thousands, prior to a final recruitment ratio of 1 patient in 17 approached to participate in the study, then a further drop-out rate of 25% after consent,

the patient population to draw these numbers from would need to be at least national, if not international. Furthermore, the waiting time for weight loss surgery was up to 12 months in some cases, which coupled with the length of follow-up required to observe a change in kidney function, may make the study prohibitively lengthy.

A protracted study would be expensive given the level of staffing required to adequately conduct screening and provide study information to potential participants in a timely manner given the potentially very large target population required to recruit an adequate number of participants. After recruitment, the time required for surgical wait-listing and follow-up would be lengthy, and the high cost of staffing multiple centres with professionals to deliver lifestyle modification programmes and post-surgical dietary education, plus research support staff to undertake blinded data collection, may be unaffordable. The benefits of the study findings would need to be adequately balanced against the costs of conducting such a study.

Furthermore, prior to any such study being conducted, the measure of kidney function in obese patients with CKD, iohexol clearance GFR or otherwise, would been to be validated in the target population, both internally for reliability, and externally against the gold standard inulin clearance method. In retrospect, the battery of measures undertaken in the present pilot study was too extensive, even for an exploratory study. A study primarily examining the relationship between weight loss and kidney function could be limited to the primary outcome and patient-focused outcomes only, such as quality of life, with the majority of the mechanistic markers omitted, especially given the likelihood of a very extensive sample size required to provide adequate power to elicit a significant intervention effect. Adiponectin, leptin, HOMA-IR and possibly fetuin-A may be helpful if a "reverse" translational approach was adopted which would lead to further mechanistic studies, to

elucidate the mechanisms involved. The low level of inflammation in the study participants was not expected and may reflect the inadequacy of eGFR as a measure of kidney function in obese patients with stages 3-4 CKD, and the added value of inflammatory markers in addressing the primary outcome is negligible.

One such trial is indeed planned, as our clinical research team was recently contacted by Professor Vincent Esnault, from the Departments of Nephrology and Clinical Immunology, Nantes University Hospital, Nantes, France, regarding the potential pooling of data from the present study, with the planned French multi-centre study. This planned study is adopting a similar protocol, hoping to recruit 100 patients in France, randomising them to either weight loss surgery or standard care (personal communication Professor Vincent Esnault, 2012). Even if the full sample size for this study to determine the effect of weight loss surgery on kidney function is achieved, it is unlikely to be powered to explore the secondary relationships best determined though multiple linear regression models using mixed methods analysis.

Problems associated with conducting a randomised controlled intervention study

Problems were also identified in controlling the multicomponent interventions, such as the WMP included as part of best medical care. The WMP is a multi-disciplinary, structured intervention using diet, exercise and pharmacotherapy, delivered using behavioural therapy techniques. The requirements of the research data collection did not correspond with the practicalities of research patients joining an existing clinical service, and not all patients were able to experience the full benefit of the WMP, and were unable to see the physiotherapist at every clinic visit. Fasting blood measures were optimally taken in the morning, which made it difficult for patients with other commitments to also attend corresponding WMP appointments in the afternoons. Furthermore, orlistat became

unavailable half-way through the study, an occurrence which was unable to be controlled by the researchers, and compromised the integrity of the WMP as a package of care, and no alternative medication was available.

Compliance with the WMP appeared poorer in this study than is usually apparent in routine clinical practice. Several factors may have contributed to this, such as the type of patient enrolling in the study may have been atypical for the WMP, as patients participating in a randomised controlled study for surgery may have preferred surgical treatment, and may have been less motivated to engage with the necessary dietary and exercise changes needed for successful weight loss without surgery. In routine clinical practice, patients are required to complete and return a 7-day food and activity diary prior to participating in the WMP, and this particular criterion was removed in the present study. In a similar, but non-randomised, study of surgery compared to lifestyle weight loss treatment, compliance may have been better since patients self-selected their treatment group, and the lifestyle treatment group had a period of residential treatment, which impacted upon food and activity choices (Hofso, Nordstrand et al. 2010).

Compliance with the patients' usual prescribed medications was variable during the study. Variable compliance may have confounded the insulin resistance and BP results, and the cessation of the production of orlistat during the study also may have impacted upon weight loss and blood lipids. Even with extremely careful recording of BP medications and standardised measurement of BP, non-compliance with medication for known hypertension during the study, may have impacted upon the results for associations between weight loss and hypertension, and proteinuria, particularly in this study with a small number of participants. The use of HOMA-IR as a measure of insulin resistance in patients both with and without diabetes, may have been problematic. Even though

patients attended data collection visits in a fasted state and without administering their usual insulin dose, insulin levels were still very high in some patients. There was only a small change in HOMA-IR evident throughout the study, despite significantly more weight loss in the SG group.

The weight regain after 6 months in the BMC group, may have been related to changes in physical activity status in some patients in this group. One patient developed a condition requiring non-weight bearing immobilization of the foot in a plaster cast from month 9 until the end of the study, one patient moved to a new area and felt unsafe exercising out-of-doors and did not find an indoor alternative. Furthermore, another patient in the BMC group developed a concurrent undiagnosed condition with pain behind the eyes, which made focusing on weight loss difficult for the patient, and distracted from weight loss, and one patient did not attend any Weight Management Programme appointments.

Summary and conclusions

Use of both a structured lifestyle modification programme and LSG surgery resulted in significant weight loss after 12 months in obese patients with stages 3-4 CKD. Weight loss was associated with improvements in quality of life scores, and both weight loss and reduction in fat mass were related to an increase in adiponectin across both intervention groups. LSG weight loss was associated with positive changes in adipokines, and lifestyle weight loss was associated with a reduction in triglycerides. Estimated kidney function using the 4-variable MDRD study equation greatly underestimated kidney function. Weight loss may improve kidney function in obese patients with CKD, although methods of measuring kidney function in obese patients with CKD should be validated before further intervention studies are undertaken in this area.

Clinical intervention trials, particularly, those with multi-component interventions are difficult to conduct and to control adequately. Further observational research could be conducted on a national and international scale to provide more extensive safety and efficacy data on the effects of intentional weight loss in obese patients with CKD.

Chapter 6: Prevalence of Chronic Kidney Disease by Body Mass Index in the Health Survey for England 2010 and in patients with Acute Coronary Syndromes in England and Wales

Chapter summary

Cross-sectional and longitudinal studies in European, North American and Japanese populations have demonstrated that obesity is a risk factor for chronic kidney disease (CKD). Studies examining the relationship between obesity and CKD in the United Kingdom (UK) have been conducted in local populations, but there are no studies evaluating the risk of CKD with overweight and obesity in a nationally representative sample in the UK. The aim of this study was to determine if overweight and obesity are independently associated with the prevalence of CKD in two national datasets, the Myocardial Infarction National Audit Project (MINAP) and 2010 Health Survey for England (HSE) cohorts. Data was examined retrospectively from 2 prospectively collected national data sets. CKD was defined as estimated kidney function < 60 ml/min/1.73m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula using serum creatinine, age, gender and race variables. As previous studies used the Modification of Diet in Renal Disease (MDRD) study equation to estimate kidney function, the analysis was repeated with this definition to allow comparisons. Multivariable logistic regression models were developed to calculate odds ratios (OR) and 95% confidence intervals (CI) for CKD risk by BMI categories. The BMI reference category was 18.5 kg/m^2 – 24.9 kg/m^2. The relationship between obesity and the risk of CKD could not be determined in the MINAP population as the complete dataset was less than 10% of the initial sample and may not be representative of the MINAP population in its entirety. The prevalence of CKD was 5.9% in the HSE 2010 population, which was similar to previous studies. The risk of CKD was over 2.5 times higher in obese participants,

compared to normal weight participants in the HSE 2010 study population, after adjustment for age, gender, ethnicity, smoking, diabetes and hypertension (adjusted OR 2.78 (95% CI 1.75 to 4.43) for BMI 30.0 - 39.9 kg/m^2; adjusted OR 2.68 (95% CI 1.05 to 6.85) for BMI ≥ 40.0 kg/m^2). The risk for CKD increased with increasing BMI in the UK population, supporting the findings from previous epidemiological studies. Given the relatively low prevalence of CKD compared to obesity, and it remains unclear whether obesity increases prevalence of CKD early in the course of CKD, or accelerates progression, or both, yet recent evidence suggests a latent effect, which may account for at least some of the differential findings in previous studies. Future service delivery planning should account for possible latent increases in CKD in the years following an epidemic rise in population obesity rates.

Introduction

Obesity has been demonstrated to be a novel risk factor for prevalent CKD, and the development of CKD and end stage kidney failure over time, in North American, Japanese, Thai, and European populations (Fox, Larson et al. 2004; Gelber, Kurth et al. 2005; Kramer, Luke et al. 2005; Hallan, de Mutsert et al. 2006; Hsu, McCulloch et al. 2006; Foster, Hwang et al. 2008; Kawamoto, Kohara et al. 2008; Munkhaugen, Lydersen et al. 2009; Satirapoj, Supasyndh et al. 2012). This relationship has not been well investigated in national population studies within the United Kingdom (UK). To date, there are only 5 published studies examining the association between obesity and CKD in the UK, all of which are in local, not national, population samples (Othman, Kawar et al. 2009; Hobbs, Farmer et al. 2011; Brown, Mohsen et al. 2012; Burton, Gray et al. 2012; Mohsen, Brown et al. 2012). In a recent cross-sectional study of a population of 61 000 primary care patients in Kent, South East England, the relationship between an eGFR of < 60/ml/ min/1.73m^2

(MDRD study equation) and BMI was examined (Hobbs, Farmer et al. 2011). The authors showed a statistically significant trend for a difference in eGFR across BMI categories using an analysis of variance ($p<0.001$). However, the authors reported that as this difference was small and not evident once BMI was greater than 25 kg/m^2, it was unlikely to be biologically significant. 2 separate logistic regression models were created, both adjusted for age, gender, diabetes and hypertension, but not ethnicity, in patients with an eGFR of < 120 $ml/min/1.73m^2$ and < 60 $ml/min/1.73m^2$, and with BMI as a continuous variable. The results display models stratified by age but do not state what the age range reference category is, and are difficult to interpret. Crucially, there appears to be no estimate of the odds ratio for the risk of CKD, defined by an eGFR < $60ml/min/1.73m^2$, with BMI as a categorical variable; which limits comparisons between this study and previous studies in non-UK populations (Kramer, Luke et al. 2005; Hallan, de Mutsert et al. 2006; Kawamoto, Kohara et al. 2008). The second UK population cross-sectional study examined the relationship between measures of obesity and CKD in almost 6 500 randomly selected patients without diabetes from General Practices in Leicestershire (Burton, Gray et al. 2012). The risk of CKD increased with increasing BMI (OR 1.04, 95% confidence interval 1.02 to 1.05; $p < 0.0001$), yet the level of increased risk was small, and did not change after adjustment for other known CKD risk factors including age, gender, albuminuria and hypertension.

There are 3 longitudinal studies examining the relationship between baseline BMI and progression of established CKD in UK local populations (Othman, Kawar et al. 2009; Brown, Mohsen et al. 2012; Mohsen, Brown et al. 2012). Baseline BMI was found to predict CKD progression in 125 patients with an eGFR < 60 $ml/min/1.73m^2$, over a median follow up period of 9 years (Othman, Kawar et al. 2009), but did not predict progression of CKD in over 700 patients, also with an eGFR < 60 $ml/min/1.73m^2$, over 3

years (Brown, Mohsen et al. 2012; Mohsen, Brown et al. 2012). It is likely that 3 years of follow up may have been inadequate to examine the relationship, and only 2 measures of eGFR were used in the latter studies, which may not be sufficient to observe change, given the normal variation in eGFR (Chang and Kramer 2012).

The primary cause of the kidney disease may alter the rate of CKD progression. Obesity related glomerulopathy, with its associated glomerular lesions and podocyte hypertrophy (Serra, Romero et al. 2008), might progress at a slower rate than CKD primarily due to hypertension or diabetes with obesity as a secondary factor (Kambham, Markowitz et al. 2001). Recent evidence suggests that it is the duration of obesity that is predictive of development of CKD, indicating that progression to overt CKD with a decline in eGFR occurs over many years (Silverwood, Pierce et al. 2013). The difference in progression rates between primary and secondary obesity related CKD could impact on the relationship observed between obesity and the progression of CKD in longitudinal studies.

Furthermore, the duration and severity of the hypertension or complications of diabetes at entry into the study, and/or the successful control of hypertension and blood glucose levels, irrespective of BMI, may also impact on the rate of disease progression, and these factors may be difficult to control for in large studies. For example, severe uncontrolled hypertension with mild obesity is likely to result in the development of CKD faster than severe obesity with mild hypertension, yet in studies using categorical data at least, these differences may be difficult to distinguish.

In recent years, 2 large, prospectively collected, national data sets have included a single serum creatinine measure, together with data on age, gender, ethnicity and BMI, providing an opportunity to determine the prevalence of CKD in these populations and the risk of

CKD associated with BMI. In 2010, the Health Survey for England included serum creatinine (from which eGFR can be calculated) in the dataset to assist in determining the prevalence of CKD in the population (Roth, Roderick et al. 2011). This dataset provides a randomly selected general population sample (Craig and Mondell 2011), which may include both healthy individuals and those with acute and chronic illnesses, in which to explore the relationship between obesity and the CKD at a whole population level.

The Myocardial Ischemia National Audit Project (MINAP) database holds prospectively collected, anonymous data on the management of acute coronary syndromes from all National Health Service (NHS) hospitals across England and Wales since 2000. As the NHS is the predominant provider of immediate clinical management post acute myocardial infarction, MINAP is a unique dataset on a contemporary population-based cohort of patients with acute coronary syndromes (Herrett, Smeeth et al. 2010).

There is considerable overlap in the known risk factors for CKD and CVD, notably, diabetes, hypertension, dyslipidaemia and obesity (Levey, Coresh et al. 2003; Gelber, Kurth et al. 2005), and these factors are the components of metabolic syndrome (Grundy, Cleeman et al. 2005). Similarly, CKD is associated with progressively increasing cardiovascular disease (CVD) risk as kidney function declines (Vanholder, Massy et al. 2005). As CKD and CVD appear to be intricately linked, and the risk of developing one increases with the other, the MINAP database is likely to contain a significant proportion of patients with CKD, and therefore, presents itself as a useful tool with which to explore the relationship between obesity and CKD in a UK based population with existing cardiovascular disease.

Study Aim

This study aims to determine if the risk of CKD increases with overweight and obesity in two nationally sampled UK datasets - the Health Survey for England 2010, and the MINAP database, to verify the evidence of this relationship in European and US populations.

Primary hypothesis

Overweight and obesity are independently associated with the risk for CKD (eGFR < 60 ml/min/1.73m^2) in both the general population and in a cohort of adults with cardiovascular disease in the United Kingdom.

Methods

This was a retrospective cohort study of 2 prospectively collected national data sets.

Study Population and Setting

Data were extracted from the anonymised Health Survey for England 2010 and the MINAP database of adults with acute coronary syndrome events from all NHS hospitals managing these patients in England and Wales (n=242) between January 2008 and April 2010. The Health Survey for England is carried out by the Joint Health Surveys Unit of the National Centre for Social Research (NatCen) and the Department of Epidemiology and Public Health at the University College London (UCL) Medical School (Craig and Mondell 2011). During the initial data collection visit, with participants' consent, a second visit with a nurse is arranged for physical measurements, and collection of blood, saliva and urine samples. The Health Survey for England data set includes a vast array of information, including demographics, socio-economic status, self reported dietary

information, medications, co-morbidities, and mental health measures. In the Health Survey for England 2010 population, the study included adult participants over 18 years, with a valid serum creatinine measurement and calculable BMI.

The current MINAP dataset includes information on pre- and in-hospital treatment, patient demographics, previous medical history and vital status. Data are collected by nurses, doctors and clinical audit staff at the participating hospitals and entered into a dedicated database. Data quality is assessed annually using a validation tool requiring hospitals to re-submit a random subset of records to measure the agreement between the original record and re-submitted data. The study was limited to adult patients with non-ST elevation myocardial infarction (nSTEMI) acute coronary syndrome, the commonest type of acute coronary syndrome observed in the MINAP population.

Use of the MINAP study database was approved by the South East London Research Ethics Committee 2 (11/LO/0246) the Health Survey for England data was accessed from the Economic and Social Data Service at the UK Data Archive for use in the present study (National Centre for Social Research and Royal Free and University College Medical School. Department of Epidemiology and Public Health 2012). Ethical approval to use the Health Survey for England dataset was not required as it is an anonymised, publicly available set of data provided by the UK Data Archive for the purposes of research and education.

Main Outcome and Measures

The primary outcome was the risk of concomitant CKD, defined as eGFR < 60 ml/min/1.73m^2, as BMI increases in the Health Survey for England 2010 and MINAP

nSTEMI acute coronary syndrome populations with both BMI and a single serum creatinine measure recorded.

Collection of a single serum creatinine value obtained on hospital admission is part of the routine MINAP data set for each individual, and was also included in routine data collection in the Health Survey for England in 2010. Blood samples were analysed and serum creatinine values were obtained in a single laboratory in the Health Survey for England, and in the MINAP study serum creatinine values are standardised to an isotope dilution method mass spectrometry method so serum creatinine values collected at different data collection sites are comparable. Kidney function was defined as estimated glomerular filtration rate (eGFR) in ml/min/1.73m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula using serum creatinine, age, gender and ethnicity variables (Levey, Stevens et al. 2009). Kidney function was subsequently categorised using the Kidney Disease Outcomes Quality Initiative (KDOQI) stages of CKD (2002), and CKD was classified as CKD stage 3 or above, with an eGFR of < 60 ml/min/1.73m^2.

The CKD-EPI equation, developed using data from ten pooled studies with measured GFR and validated from a separate database of a further sixteen studies, is more accurate than the Modification of Diet in Renal Disease (MDRD) study equation, with a lower bias at higher estimates of GFR due to the use of a linear spline term, not present in the MDRD study equation (Levey, Stevens et al. 2009). The CKD-EPI equation was validated on a broader population than the MDRD study equation and improves the general applicability, as well as decreasing the false positive rate of classification of stage 3 CKD (Levey, Stevens et al. 2009). The CKD-EPI equation, developed in 2009, has not yet been widely adopted as the preferred method for estimating GFR, but may become the

preferred estimation equation in future if further validation studies support the initial findings (MacGregor and Taal 2011). The Health Survey for England dataset included both creatinine and eGFR using the MDRD study equation (Roth, Roderick et al. 2011), so serum creatinine values were used to re-calculate eGFR using the CKD-EPI equation for the present study.

BMI was calculated as weight (kg)/height (m) x height (m) from hospital measured height and body weight, recorded in routine MINAP data collection, and from nurse measured height and weight in the Health Survey for England 2010, and categorised into underweight, normal range, overweight and obese classifications according to the World Health Organisation (WHO) criteria (World Health Organisation 2006). Diabetes, and hypertension status data were collected routinely as part of both data sets. Diabetes was classified as a previous diagnosis of diabetes and/or the use of an oral hypoglycaemic agent or insulin, and/or fasting blood glucose > 6.7 mmol/L and/or a random blood glucose of > 11 mmol/L prior to admission (2011). Hypertension was classified as already receiving treatment (drug, dietary or lifestyle) for hypertension or with a recorded blood pressure of >140/90 measured by the survey nurse in the Health Survey for England (Craig and Mondell 2011), or recorded on at least two occasions before admission in the MINAP data set (2011). Smoking status was defined as never smoked (reference category), ex-smoker and current smoker.

Statistical analyses

Statistical analysis was completed using STATA version 11 (StataCorp: College Station, TX) and SPSS version 19 (IBM: Armonk NY). Descriptive statistics were expressed as mean (SD) or median (interquartile range IQR) for parametric and non-parametric continuous variables, respectively. Categorical variables were expressed as percentages.

Baseline comparisons between continuous variables were performed using Student's T-test or Mann-Whitney U test for parametric and non-parametric variables, respectively, and Pearson's chi-squared (χ^2) test for categorical variables. Normality of the data sets was established using visual assessment of histograms representing a normal curve, and non-parametric continuous variables were converted into categorical variables.

Patients with both a single serum creatinine value and calculated BMI between 15-60 kg/m^2 were included in the study. BMI outside this range was deemed to be either incorrect or not representative of population norms and was therefore excluded. Baseline characteristics in both populations, with an estimate of kidney function using the CKD-EPI equation, were reported, including age, gender, ethnicity and eGFR, and diabetes and hypertension status.

Patients and survey participants were split into 2 groups according to estimated kidney function. The CKD group had an eGFR < 60 $ml/min/1.73m^2$, and the non-CKD group had an eGFR ≥ 60 $ml/min/1.73m^2$. Baseline characteristics of the two groups were compared for age, gender, ethnicity, diabetes and hypertension. Patients in both groups were classified by WHO BMI criteria of underweight (< 18.5 kg/m^2), normal range (18.5 – 24.9 kg/m^2), overweight (25 - 29.9 kg/m^2), obese classes I and II (30.0 - 39.9 kg/m^2), and obese class III (≥ 40 kg/m^2). The distribution of patients across BMI categories, in the CKD group and the non-CKD group were compared using Pearson's chi-squared test.

To evaluate the relationship between CKD and obesity in the each study population, whilst accounting for other patient characteristics and conditions, multivariable logistic regression models were developed to calculate OR and 95% CI. The BMI reference category was 18.5 kg/m^2 – 24.9 kg/m^2. The unadjusted model (model 1) was sequentially built upon to

include the pre-determined co-variables age, gender and ethnicity (model 2), plus smoking status diabetes, and hypertension (model 3).

Results

The MINAP population data from 1st January 2008 to 1st April 2010 included 181 490 patients with an acute coronary syndrome. 47 094 patients were excluded as they had missing data on age, gender, ethnicity or serum creatinine, and therefore, estimated kidney function could not be calculated. A dataset of 36 598 patients with nSTEMI events, with complete data for age, gender, blood pressure, diabetes, hypertension, cardiovascular co-morbidities and previous cardiac interventions or procedures, serum creatinine, and index of multiple deprivations score was created for a separate study analysing the likelihood of intensive or conservative intervention treatment post nSTEMI in patients with, and without, CKD (classified by NKF-KDOQI CKD stage). 25 743 patients were excluded with missing data for height, and/or weight, or with a calculated BMI of < 15 kg/m^2, leaving a total of 10 855 patients in the dataset for the present study (Figure 22).

As this data set was less than 10% of the original sample, it was deemed inappropriate to continue the analysis further on the MINAP population, as the sample may not be representative of the entire MINAP population.

The Health Survey for England 2010 study population included 8 420 adults and 5 692 children. This study was limited to adult participants so all children were excluded. 4 957 of the 8 420 adult participants were excluded due to missing serum creatinine, height, weight, ethnicity, gender, hypertension or diabetes status information, leaving a study

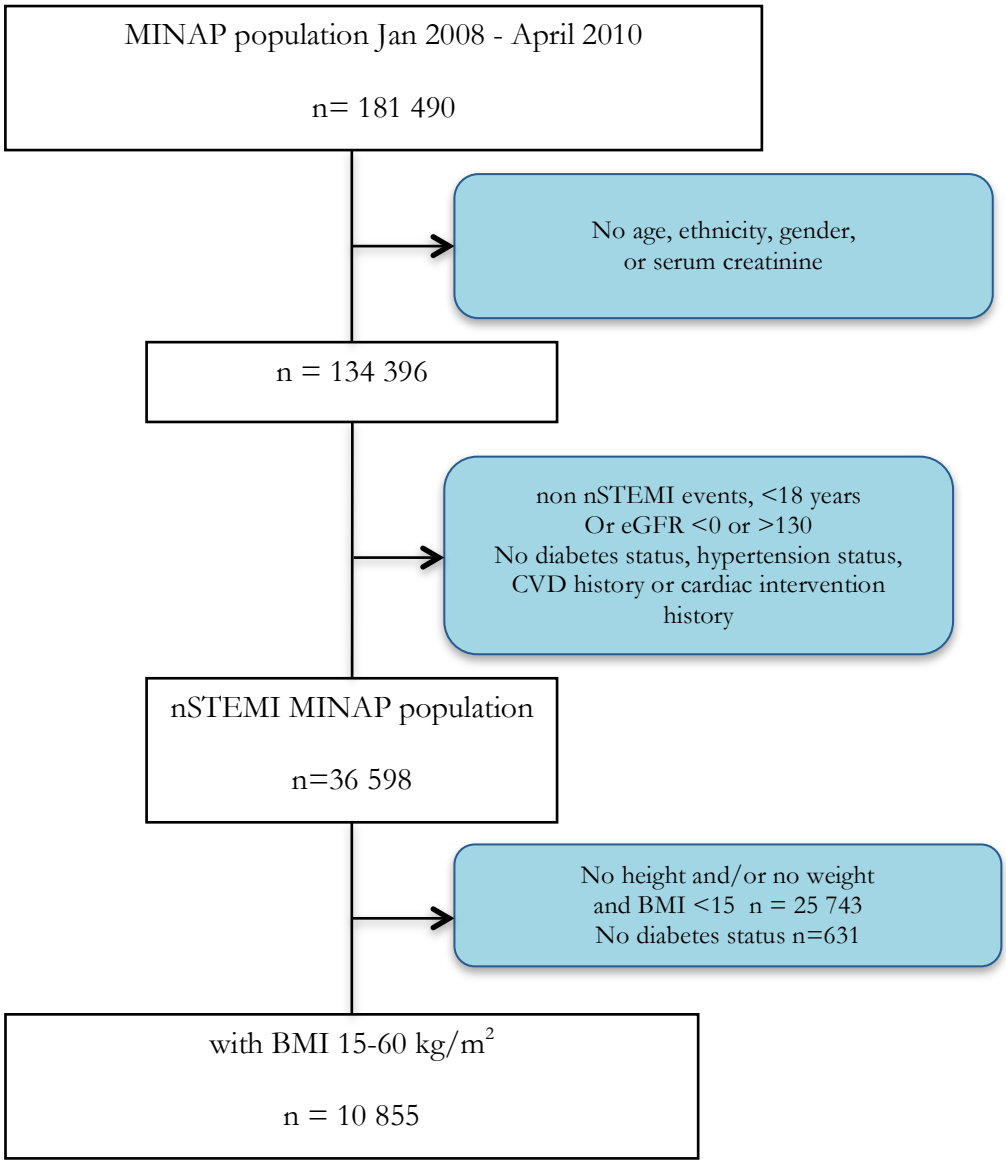


Figure 22: Selection of study population from MINAP database
BMI, body mass index; eGFR, estimated glomerular filtration rate

sample population of 3 463 adults with a valid BMI and calculable eGFR (Figure 23); equivalent to 41.1% of the original adult study population. The characteristics of the Health Survey for England study population are presented in Table 27.

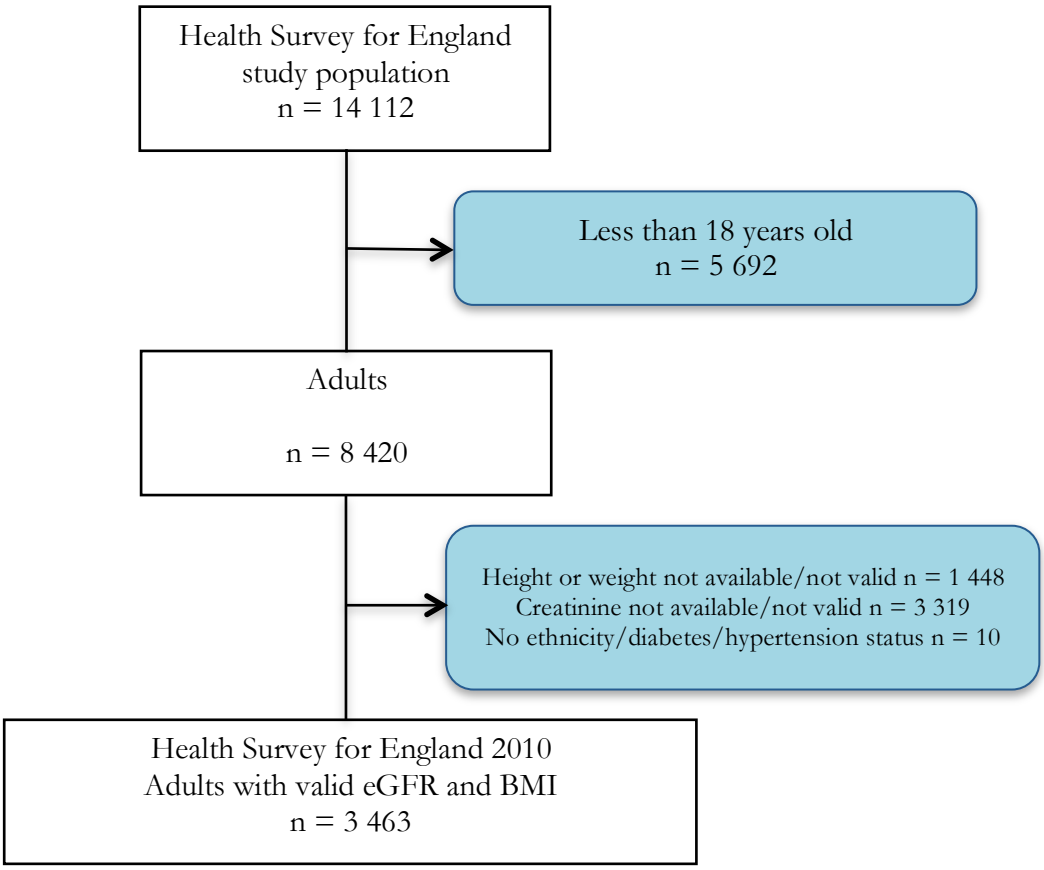


Figure 23: Selection of study population from Health Survey for England 2010
BMI, body mass index; eGFR, estimated glomerular filtration rate

Table 27: Characteristics of the Health Survey for England 2010 study population with valid BMI and CKD-EPI equation estimated kidney function (n = 3 463)

Age	51.1 (±16.7) years
Gender	44.2% Male; 55.8% Female
Ethnicity	92.8% White, 1.9% Black, 3.3% Asian, 2.0% Other
Diabetes	6.0%
Hypertension	24.8%
CKD-EPI eGFR	93.0 (±19.3) ml/min/1.73m^2
BMI	27.6 (±5.2) kg/m^2

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

Table 28 displays the distribution of BMI in the Health Survey for England 2010 participants. Over 65% of the population were overweight or obese.

Table 28: Distribution across body mass index categories for the Health Survey for England 2010 population with valid BMI and CKD-EPI equation estimated kidney function (n = 3 463)

Body Mass Index (BMI) category (kg/m²)				
<18.5	18.5-24.9	25.0-29.9	30.0-39.9	≥40.0
29 (0.8%)	1114 (32.2%)	1380 (39.9%)	852 (24.6%)	88 (2.5%)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration;

204 (5.9%) participants in the Health Survey for England 2010 had an eGFR < 60 ml/min/1.73m^2 and were thus defined as having CKD. Mean age and BMI and gender, ethnicity, diabetes and hypertension status, and BMI are described in Table 29.

The Health Survey for England population with CKD were older, had more diabetes and hypertension, and a higher mean BMI than those without CKD. The non-CKD group had greater representation from Black, Asian and other ethnic groups than the CKD group. The higher levels of diabetes and hypertension in the CKD group were expected, as these are known risk factors for the development of CKD.

Table 29: Description of the Health Survey for England 2010 study population defined by CKD status[a]

	Non-CKD group **eGFR ≥ 60 ml/min/1.73m²** **n = 3 259**	**CKD group** **eGFR < 60 ml/min/1.73m²** **n = 204**	**p**
Age (years)	49.7 (± 16.0)	73.0 (± 11.6)	< 0.001
Gender (Male)	44.3%	44.1%	0.96
Ethnicity	92.5% White, 2% Black, 3.5% Asian, 2% Other	98.5% White, 0% Black, 1.0% Asian, 0.5% Other	0.03
Diabetes	5.3%	16.7%	< 0.001
Hypertension	22.7%	57.4%	< 0.001
BMI (kg/m²)	27.5	29.3	< 0.001

[a] data presented as mean (± standard deviation) or prevalence; (BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

The distribution of participants across BMI categories, by CKD group, in the Health Survey for England 2010 population is presented in Table 30. There were more normal weight and overweight participants in the non-CKD group, than in the CKD group. Conversely, the CKD group had a greater percentage of obese patients than the non-CKD group. The distribution of BMI was not the same in the CKD and non-CKD groups (χ^2 = 30.85, degrees of freedom = 4, $p < 0.001$).

Table 30: Distribution across BMI categories by CKD status in the Health Survey for England 2010 study population

CKD status		BMI category (kg/m²)				
		<18.5	18.5-24.9	25.0-29.9	30.0-40.0	>40.0
Non-CKD group (eGFR ≥ 60 ml/min/1.73m²)	n = 3 259	0.8%	33.1%	40.0%	23.7%	2.5%
CKD group (eGFR < 60 ml/min/1.73m²)	n = 204	1.0%	18.1%	38.2%	38.7%	3.9%

n = 3 463, χ^2 = 30.85, degrees of freedom = 4, $p < 0.001$

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;

The unadjusted and adjusted odds ratios and 95% confidence intervals for the risk of CKD as BMI increases are displayed in Table 31. The risk of developing CKD increases as BMI increases in the Health Survey for England 2010 population. In the unadjusted model (model 1), the risk of CKD is almost 3 times higher in those with a BMI of 30 - 39.9 kg/m^2 than in those with normal BMI. After adjustment for age, gender and ethnicity (model 2), the risk is attenuated, but remains significant, for the overweight group, and the risk increases with a BMI ≥ 30 kg/m^2. With further adjustment for smoking, diabetes, and hypertension (model 3), the risk of CKD is mitigated slightly, but remains over 2.5 times higher in those with a BMI ≥ 30 kg/m^2, compared to those of normal weight. In the overweight group the risk of CKD is fully attenuated by adjusting for diabetes, hypertension and smoking status.

Table 31: Logistic regression models for risk of concomitant CKD (CKD-EPI eGFR< 60 ml/min/1.73m²) by body mass index (BMI) in the Health Survey for England 2010 study population

n = 3 463	**β (Odds Ratio) and 95% Confidence Interval** Model 1 -unadjusted	**β (Odds Ratio) and 95% Confidence Interval** Model 2 - adjusted for age, gender and ethnicity	**β (Odds Ratio) and 95% Confidence Interval** Model 3 - adjusted for age, gender, ethnicity smoking, diabetes and hypertension
BMI < 18.5 kg/m²	2.16 (0.50 to 9.43)	2.28 (0.30 to 17.16)	2.08 (0.27 to 15.74)
18.5 - 24.9 kg/m²	1.00	1.00	1.00
25.0 - 29.9 kg/m²	1.75 (1.17 to 2.61)**	1.57 (1.01 to 2.44) *	1.48 (0.94 to 2.31)
30.0 - 39.9 kg/m²	2.98 (2.00 to 4.46)***	3.14 (2.00 to 4.92)***	2.78 (1.75 to 4.43)***
≥ 40.0 kg/m²	2.92 (1.31 to 6.47)**	3.42 (1.37 to 8.56)**	2.68 (1.05 to 6.85)*

*** p < 0.001; ** p < 0.01; * p < 0.05; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate

In order to make comparisons with other studies, this analysis was repeated using the MDRD study equation to calculate eGFR (Levey, Bosch et al. 1999; Levey, Greene et al. 2000), and the results did not change markedly – although risk is lower and becomes non significant when BMI ≥ 40.0 kg/m^2 (Table 32). The prevalence of CKD in the study population defined by the MDRD study equation was 7.4% (n = 254), with 38.1 % of those with CKD with BMI ≥ 30 kg/m^2 compared to 42.6% using the CKD-EPI equation.

Table 32: Logistic regression models for risk of concomitant CKD (MDRD eGFR< 60 ml/min/1.73m²) by body mass index (BMI) in the Health Survey for England 2010 study population

n = 3 463	**β (Odds Ratio) and 95% Confidence Interval** Model 1 -unadjusted	**β (Odds Ratio) and 95% Confidence Interval** Model 2 - adjusted for age, gender and ethnicity	**β (Odds Ratio) and 95% Confidence Interval** Model 3 - adjusted for age, gender, ethnicity smoking, diabetes and hypertension
BMI <18.5 kg/m²	1.53 (0.35 to 6.62)	1.81 (0.34 to 9.74)	1.73 (0.32 to 9.47)
18.5-24.9 kg/m²	1.00	1.00	1.00
25.0-29.9 kg/m²	1.70 (1.20 to 2.40)**	1.41 (0.98 to 2.03)	1.37 (0.95 to 1.99)
30.0-39.9 kg/m²	2.42 (1.69 to 3.43)***	2.14 (1.46 to 3.12)***	2.02 (1.37 to 2.97)***
≥40.0 kg/m²	2.35 (1.12 to 4.96)*	2.29 (1.03 to 5.10)*	2.01 (0.89 to 4.54)

*** p < 0.001; ** p < 0.01; * p < 0.05; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease study equation

Discussion

Obesity is associated with a significantly increased risk of CKD in a large, randomly selected, nationally representative population sample in the United Kingdom. As far as can be determined, this is the first report of an association between obesity and CKD risk in a nationally representative sample of the United Kingdom population.

The prevalence of CKD in the Health Survey for England group was just under 6% using the CKD-EPI equation, which is similar to the reported prevalence of 6% in women and 7% in men in the 2010 Health Survey for England report, using the MDRD equation (Roth, Roderick et al. 2011), and the 5% reported in the HUNT II study in Norway, with the same definition of CKD as an eGFR < 60ml/min (Hallan, de Mutsert et al. 2006).

In the present study, there were a greater percentage of overweight and obese patients in the CKD group, compared to the non-CKD group. The risk for CKD increased with increasing BMI, supporting the findings from previous epidemiological studies in European, Japanese and North American populations (Kramer, Luke et al. 2005; Hallan, de Mutsert et al. 2006; Kawamoto, Kohara et al. 2008). In cross-sectional studies of community based samples, the fully adjusted risk for CKD with obesity, compared to normal weight controls, increased by 44% in the HUNT II study population for eGFR < 45 ml/min, and by 57% when adjusted for age and gender only for eGFR < 60 ml/min (Hallan, de Mutsert et al. 2006), and the risk for CKD, with overweight and obesity combined, doubled in a Japanese community population (Kawamoto, Kohara et al. 2008). In the current study, the risk of CKD was similar, using the MDRD equation, yet the fully adjusted risk for CKD, using the CKD-EPI equation, was over 2.5 times as high for obese participants than normal weight controls. Although the overall percentage of participants classified with CKD was lower using the CKD-EPI equation than the MDRD equation,

there was a greater proportion of obese participants in the CKD-EPI classified CKD group than in the MDRD defined CKD group.

In patients with known risk factors, the fully adjusted risk of CKD with obesity was 23% higher in patients with hypertension (Kramer, Luke et al. 2005), indicating that the added risk of obesity is lower in populations with other previously identified risk factors for CKD, such as hypertension, than in studies of mixed or apparently healthy community populations. The independent risk of obesity appears greater in the "healthy" obese populations, not because the absolute risk is any higher, but because the risk in the comparator group is lower, as in the "healthy" populations, the comparator group lack other contributing risk factors for CKD, which are present in the populations with existing CVD disease and hypertension.

The results of this study differ to previous cross-sectional studies of the relationship between obesity and CKD, which were conducted in a local, rather than national United Kingdom population samples. In the previous studies, there was a very small or no relationship between eGFR and BMI in the regression models, after adjustment for age, gender, diabetes and hypertension, in samples of participants from General Practices in Kent and Leicestershire (Hobbs, Farmer et al. 2011; Burton, Gray et al. 2012). The present study demonstrated a significant effect of obesity on the odds of having CKD in the Health Survey for England 2010 population after adjustment for the abovementioned factors. These differences may reflect sampling biases in local versus national population datasets, or differences in General Practitioner derived versus randomly selected by postcode population samples. The methodology for the statistical analyses are difficult to interpret in the previous UK studies, and in one study the statistical model was not corrected for ethnicity, as it was inconsistently reported in the dataset (Hobbs, Farmer et al.

2011). Failure to include ethnicity as a baseline variable in the dataset puts the validity of the eGFR data at risk, given that ethnicity is one the required variables to calculate the MDRD eGFR value (Levey, Bosch et al. 1999; Levey, Greene et al. 2000).

The strengths of this study include the use of datasets compiled of information collected in a uniform fashion with defined terms and standardised methods of data input. The data extracted from the both datasets contain nationally representative populations of healthy participants and patients with CVD, and the analyses were corrected for known potential confounding variables including age, gender and ethnicity, and smoking status, diabetes and hypertension as co-morbidities. Data monitoring audits of the MINAP database analyse data recording in a standardised sub-set of 20 fields (Herrett, Smeeth et al. 2010). Whilst this ensures robustness of the data set for these fields, other fields, such as height and weight, remain unmonitored and prone to missing data. The dataset was substantially reduced once patients without a calculable BMI or eGFR were excluded, and as it may not have been representative of the substantive MINAP population, the dataset was excluded from further analysis. The utility of the MINAP dataset for use in an expanding array of analyses may be compromised by the extent of missing data.

The cross-sectional design used in this study to examine the relationship between obesity and CKD in UK populations has several limitations. Firstly, by design, the study cannot determine causality, or monitor the development of CKD over time. Secondly, whilst the Health Survey for England was carried out in peoples' homes, and they were apparently well at the time of the survey, it cannot be ruled out that the single creatinine measure obtained was not representative of usual kidney function for all patients. The study sample may include patients with undetected acute kidney injury (AKI), although this is unlikely, as well as those with CKD. The serum creatinine value used in the Health Survey for

England was from a single time point only, so the true definition of CKD, with repeated tests repeated over at least three months, was not met in this study, nor in any other population based study of the relationship between obesity and CKD. Furthermore, there may also be other, unconsidered and therefore unaccounted for, variables, which may affect the relationship examined.

There is a potential to misclassify participants by using an estimate of GFR calculated from serum creatinine, rather than measured GFR, and this potential is higher in obese patients, as reported in Chapter 5 and in obese patients with diabetic nephropathy (Nair, Mishra et al. 2011). Using the CKD-EPI equation reduced the proportion of patients classified with CKD, compared to the MDRD equation in the present study. However, not all studies report large differences in measured and estimated GFR in obese subjects (Michels, Grootendorst et al. 2010). In a pragmatic sample of subjects and patients with measured kidney function, serum creatinine and height, weight and ethnicity, both the CKD-EPI equation and the MDRD study equation were 86%, and 78% accurate, respectively, in overweight and obese patients, compared to measured GFR (Michels, Grootendorst et al. 2010), although the level of kidney function for the obese patients in the study was not reported, and the measured GFR was adjusted for body surface area. Measured kidney function adjusted for body surface area in obese patients may not be physiologically appropriate, and masks the increase in single nephron GFR (Delanaye, Radermecker et al. 2005).

Whilst it is established that eGFR may overestimate the risk of CKD in the obese, given the histological evidence of obesity related glomerulopathy (Kambham, Markowitz et al. 2001; Serra, Romero et al. 2008) and the increased risk of both CKD progression and end stage kidney failure with obesity (Hsu, McCulloch et al. 2006; Hsu, Iribarren et al. 2009;

Othman, Kawar et al. 2009), it is likely that kidney damage does occur secondary to obesity (Wu, Liu et al. 2006). Recent evidence suggests that onset of overweight during early adulthood or the duration of overweight, rather than absolute BMI, is associated with the risk of development of CKD in the longer term (Silverwood, Pierce et al. 2013), indicating that the effect is latent. It is possible that the latency of the effect explains much of the discrepancy in the relationship between obesity and CKD in previous studies.

Obesity may not be a completely independent factor for development of CKD, given the relatively low prevalence of CKD compared to obesity, and it remains unclear whether obesity increases prevalence of CKD early in the course of CKD, or accelerates progression, or both (Chang and Kramer 2012). Other traditional risk factors for the development of CKD, including hypertension and dyslipidaemia, often evident alongside obesity, have a greater likelihood of leading to the development of CKD (Thomas, Sehgal et al. 2011). Alternatively, there may be other mechanisms that are evident in obesity that may be exacerbated in some patients, independently of increased adiposity, such as hyperleptinaemia, hypoadiponectinaemia and inflammation, which increase the risk of developing CKD in some obese patients, and further mechanistic studies on novel risk factors, such as these, are required.

The evidence presented in this study demonstrates a concomitant relationship between obesity and CKD in a nationally representative randomly selected sample from the UK population, and supports the findings of previous studies. The implications for this finding are evident with epidemic rates of obesity in the UK (National Centre for Social Research and Royal Free and University College Medical School. Department of Epidemiology and Public Health 2012) and the relationship between obesity and the progression of CKD in large population studies (Hsu, McCulloch et al. 2006; Munkhaugen, Lydersen et al. 2009;

Othman, Kawar et al. 2009). Whilst the findings of the present cross-sectional study do not directly implicate the development or progression of CKD with increasing obesity, future service delivery planning should account for possible latent increases in CKD in the years following an epidemic rise in population obesity rates. From the preceding studies presented in chapters 2-5, it is evident that weight loss interventions in patients with CKD are complex, with lifestyle treatments offering possible protection against cardiovascular morbidity and mortality, and whilst weight loss surgery produces greater weight loss, the risk benefit profile of this intervention remains unclear in obese patients with CKD. Effective strategies for weight loss to prevent the development of CKD and possibly slow progression of existing CKD remain a priority for investigation.

Chapter 7: Discussion

Chapter summary

This final chapter presents a summary of the findings of the 5 studies included in this thesis and discusses some of the strengths and weaknesses of the different study designs and weight loss interventions explored in this body of work. A detailed discussion is presented on developing future studies of weight loss surgery interventions in obese patients with CKD, using a structured framework for research in surgical innovation. Using this theoretical framework, it is clear that further observational studies and small, randomised, controlled, feasibility trials should be undertaken to establish the safety of surgical procedures, prior to undertaking larger research studies with clinical outcomes. We have established the London Renal Obesity Network as a starting point to develop a research database for weight loss interventions in obese patients with CKD. The feasibility of conducting a large randomised controlled trial to measure clinical outcomes is explored and the difficulties incurred when conducting clinical intervention studies are discussed. Other future weight loss interventions are explored briefly and the chapter concludes with a final summary of the findings of the thesis and recommendations for refining outcome measures and enabling patients to make informed choices about weight loss treatments.

Summary of thesis findings

This body of work has broadly explored the topic of obesity in patients with chronic kidney disease. Initially, the benefits of the Renal Weight Management Programme (WMP) on cardiovascular disease risk and survival were explored in an analysis of the time to a combined event of all cause mortality, and cardiovascular morbidity, defined as myocardial infarction, stroke or hospitalisation for congestive heart failure. Compared to patients who did not commence the WMP, patients who chose to commence the WMP had a reduced

risk of the combined event; however, there was no benefit for achieving kidney transplant waitlisting. The second study was the first case series reporting on the safety and efficacy of laparoscopic sleeve gastrectomy (LSG) weight loss surgery in obese patients with CKD, with a particular focus on the utility of this procedure to reduce weight to enable otherwise eligible patients with CKD to become listed for kidney transplantation after adequate weight loss. The study found that LSG was effective for weight loss and for kidney transplantation waitlisiting, but the procedure may be associated with additional risks in patients with CKD, than had previously been reported in non-CKD populations.

These 2 studies led to the design and conduct of 2 clinical intervention studies, to further examine the use of LSG as a treatment for weight loss in obese patients with CKD. A randomised controlled pilot study of the effect of sleeve gastrectomy (SG group) or best medical care (BMC group) including a lifestyle modification programme, on kidney function, measured by iohexol clearance glomerular filtration rate (GFR), was undertaken in patients with stages 3-4 CKD. Estimated GFR (eGFR) consistently under predicted kidney function in obese patients with CKD, and the difference was greater in stage 3 CKD than in stage 4 CKD. Hyperfiltration decreased in the SG group compared to the BMC group at 12 months. When separated by CKD stage, the reduction in hyperfiltration appeared to occur predominantly in the stage 3 CKD classified patients after SG. Patients with stage 4 CKD may have demonstrated a slight trend towards an improvement in kidney function after SG, although as the number of patients was very small, and further research is required to validate these preliminary findings. Significant weight loss was achieved in both groups from baseline to 12 months, however significantly greater weight loss was achieved in the SG group compared to the BMC group after 12 months. Weight loss was associated with an improvement in quality of life indices and an increase in adiponectin. Fetuin-A decreased in both groups after 12 months. The decrease in fetuin-A

was not associated with a change in any other variable measured in the study, yet it is known that fetuin-A decreases with weight loss. Insulin resistance decreased, and antihypertensive medication dose was reduced in the SG group, and some patients in both groups demonstrated improvements in blood lipid levels. There were no major adverse events in the SG group, although 2 patients experienced dehydration requiring hospital admission during the immediate 30-day post-operative period. One patient in the BMC group developed Charcot's foot during the study, likely secondary to an increase in weight-bearing physical activity to elicit weight loss. The LSG is likely to be a safe and effective procedure for weight loss in obese patients with stages 3-4 CKD, although further studies are required to support this finding, and the potential increased risk of dehydration, compromising kidney function, should be emphasised.

The second clinical intervention study was an observational cohort study of LSG for weight loss in obese patients with end stage kidney disease on haemodialysis. This study was designed to prospectively systematically examine the safety and efficacy of LSG in patients undergoing haemodialysis renal replacement therapy, who were not listed for kidney transplantation primarily due to an elevated BMI. 18 patients entered the study, and 4 underwent weight loss surgery before the study was terminated due to safety concerns. 2 severe adverse events occurred and the study was terminated before the safety and efficacy of LSG in obese patients undergoing haemodialysis could be determined.

Finally, the relationship between obesity and prevalent CKD was studied in 2 United Kingdom (UK) populations: a nationally representative, randomly selected, sample of participants surveyed in the Health Survey for England 2010 (HSE), and a cohort of patients with known cardiovascular disease from the Myocardial Infarction National Audit Project (MINAP) database. Similar studies have previously been conducted in the United

States, Japan and Europe, and in 2 local populations in the UK, but not in any national UK population sample. There was a high level of missing data in the MINAP population dataset. The MINAP sample population with adequate data was <10% of the original MINAP population, so this study sample was excluded from the analysis, as the study cohort may not represent the original MINAP population. In the HSE population, the risk of CKD increased as BMI increased, after correction for age, ethnicity, gender, diabetes, smoking and hypertension. These results support the previously published data in healthy European and Japanese populations, and patients with hypertension in the United States.

The implications of this link between obesity and CKD in the UK are highly relevant given the rising prevalence of obesity, with 26% of adults in the 2010 HSE classified as obese (a rate almost double that reported in 1993 (Hirani 2011)), and the likelihood that this will translate into an increase in the prevalence of CKD in the future. The prevalence of stages 3-5 CKD in adults in the UK has recently been reported as 6% in men and 7% in women (Roth, Roderick et al. 2011). Obesity-related kidney damage appears to progress slowly, but nevertheless can result in end-stage CKD, so the impact upon prevalence rates of CKD may be latent (Kambham, Markowitz et al. 2001; Praga, Hernandez et al. 2001).

Overall discussion of weight loss interventions in CKD

This thesis has explored the effects of weight loss interventions in obese patients with CKD, in an attempt to begin to define possible treatments for obesity and their effects on kidney function, qualification for kidney transplantation, and quality of life measures. Furthermore, the importance of developing and implementing safe and effective weight loss interventions in obese patients with CKD on a national scale is supported by the identification of a relationship between obesity and CKD in a UK cohort.

Participation in a structured, multidisciplinary weight loss programme may be effective for reducing the risk of cardiovascular morbidity and all cause mortality in obese patients with CKD; however it is very likely that this relationship is confounded by the observational study design, as patients choosing to participate in a weight loss programme are more likely to be motivated to make lifestyle changes that may result in a reduction in cardiovascular and all-cause mortality risk. These actions may include not only dietary and physical activity changes, but may extend to greater compliance with medication and specialist clinic visits, and also engaging in fewer high-risk behaviours. However, regardless of the potential confounding factors, this study highlights that motivation is a key requirement to make lifestyle changes that improve outcomes. Alternative treatments may be needed for patients without this internal motivation to change modifiable risk factors with lifestyle focused actions, and also for those who have been unsuccessful when attempting this established pathway to reduce cardiovascular and renal risk factors.

Weight loss surgery is 1 such alternative treatment that may be beneficial for obese patients with CKD. The 2 small pilot studies undertaken in this programme of research have indicated that it is likely, in the short term at least, that LSG weight loss surgery results in greater weight loss than best medical care, and is associated with an improvement in quality of life indices, and a reduction in insulin resistance, in obese patients with stages 3-4 CKD. Greater weight loss is also likely following the LSG procedure in patients requiring haemodialysis, however, there may be a greater risk for adverse events than in patients without CKD. This preliminary finding is supported by several recent publications on the risks of all non-emergent surgery, vascular surgery and weight loss surgery specifically, in patients with CKD requiring renal replacement therapy (Gajdos, Hawn et al. 2012; Gajdos, Hawn et al. 2012; Turgeon, Perez et al. 2012). Together, these studies indicate that patients with end-stage kidney disease have a greater risk for many types of surgery, and that the

risk is not specifically related to weight loss surgery alone. The elevated risk of adverse events post-surgery is likely related to the increased cardiovascular disease risk in patients with end-stage kidney disease, with a common aetiology of compromised vascular structure and function. It remains to be determined whether weight loss surgery can have a positive effect on cardiovascular or mortality outcomes in obese patients with CKD. Indeed, it has been suggested that the beneficial effects of weight loss surgery may outweigh the increased risk of adverse events or complications (Turgeon, Perez et al. 2012), and one such scenario where this may be relevant is in obese patients requiring dialysis who are not able to qualify for kidney transplantation waitlisting due to their elevated BMI. It is also possible that in patients with earlier stages of CKD, the benefits of weight loss surgery may outweigh the risks, if improvements in kidney function and quality of life, evident in the pilot study in chapter 5, are borne out in larger studies in future.

Design of future research and theoretical framework for surgical research

Given the experience conducting the pilot study of LSG in obese patients undergoing haemodialysis in Chapter 4, with the early cessation of the research due to 2 adverse events and the above, more recent publications on the risk of elective surgery in patients undergoing haemodialysis treatment, the design of future research studies of weight loss surgery in obese patients with CKD must be carefully considered. It seems prudent to recommend a passive observational study design, in which only patients already referred for, and accepting LSG weight loss surgery would be included, perhaps together with a second group of patients not referred for surgery, to be followed as controls, although this additional group adds another layer of complexity to any proposed study of this format.

The strengths of this design include the elimination of possible coercion into a treatment group in a study where the risks of the proposed intervention may outweigh the benefits,

as the long-term benefits are not yet known. Any decision made by a participant to undergo weight loss surgery would be made prior to the same patient being approached to participate in the study. A true observational study design would also reduce the risks attributable to the study itself, as the weight loss surgery would not be a study procedure. Additionally, such a study may be more easily conducted on a national or international scale, and indeed, a large sample size is likely to be required to adequately examine safety. In order to minimise confounding, a prospective study design is recommended, as although retrospective data can be collated more quickly, in a prospective design, both the surgical intervention itself, and the peri-operative management of factors including diet, fluids and medication adjustments could be standardised, although this may be difficult in a truly observational study. Furthermore, if the LSG procedure is deemed reasonably safe, data generated on efficacy as a secondary outcome would be useful to determine the sample size required in an interventional study, such as a randomised controlled trial.

Other factors to consider with this study design are co-morbidities and kidney function at baseline. It would be prudent to predetermine study entry criteria and separate patients with diabetes, from those without, a priori, as the risk factors in each group of patients may be different. Additionally, it has been demonstrated in these studies that the risk of the LSG specifically, and weight loss surgery generally (Turgeon, Perez et al. 2012), may increase as CKD progresses from earlier to more advanced stages.

There are inherent weaknesses to this type of study design. Primarily, causality cannot be determined, and even if a control group is included there are problems involved with matching these 2 groups, primarily the reasons why 1 group was referred and listed for weight loss surgery, and why the other group was not. Differences between these groups could include age, co-morbidities, baseline BMI, likelihood of kidney transplantation

waitlisting, and importantly, as discussed earlier, patient motivation to comply with treatment, including medication compliance. Secondly, there are ethical considerations relating to the safety of the procedure, which need to be addressed. Is a weight loss surgery procedure, that has been deemed high risk in patients undergoing dialysis, safe enough to be offered as "standard care" outside a controlled research study, before it has been adequately examined with appropriate safety studies? The introduction of new drugs requires a stepped series of phased clinical trials prior to use, after approval by the drug regulatory authorities, and yet surgical procedures are not subject to this same level of rigour.

The balance between ethical considerations for protecting patients, and the development of novel treatments, may be best explored at this point, using a theoretical framework for surgical studies. The current paradigm for investigating new medicines, with phased studies moving from measuring safety in a small group of healthy subjects in phase 1, to randomised controlled trials in phase 3 and ongoing efficacy studies and pharmacovigilance in phase 4, is difficult to translate directly, as surgical and lifestyle interventions are complex and have multiple components that cannot be separated out and controlled as easily as in a pharmacological intervention (Ergina, Cook et al. 2009).

Surgical interventions, and other complex interventions including dietary studies and other lifestyle modifications such as exercise, are multifaceted, and usually involve multiple factors, any of which may alter the result of the treatment or procedure. Figure 24 illustrates the levels and layers of surgical interventions, from the procedure itself at the centre, which is dependent on the skill of the surgeon, the nursing team, and the condition of the individual patient, out to the pre- and post-operative care, and the interdependent effects of the medical and anaesthesia teams (Ergina, Cook et al. 2009).

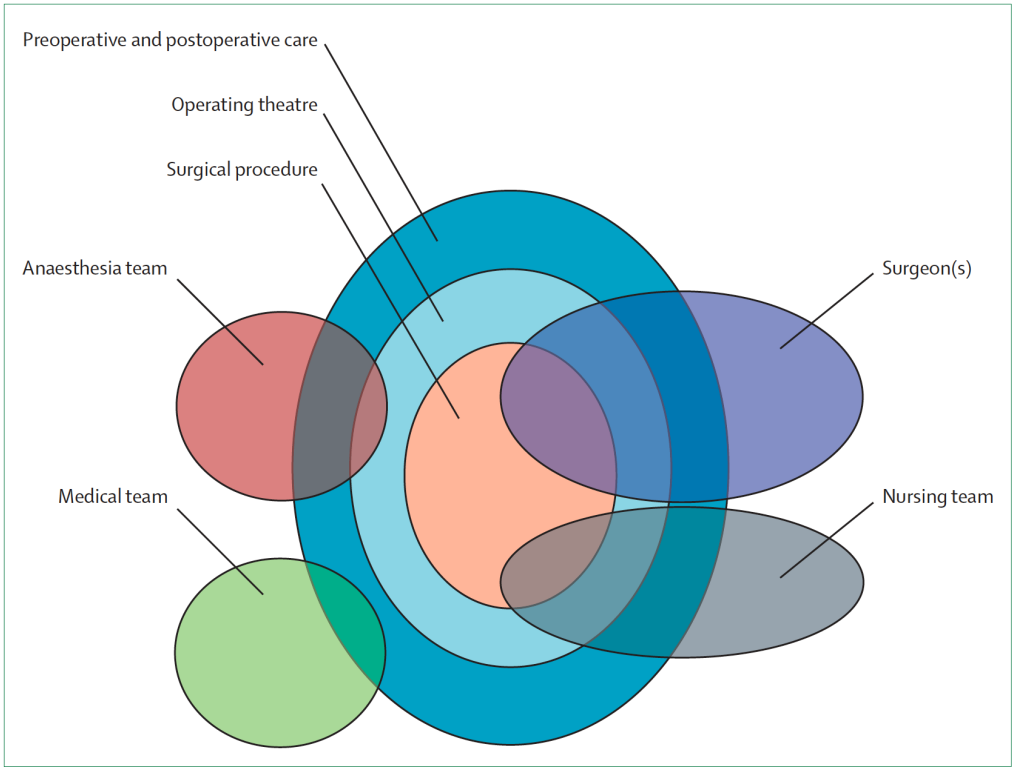


Figure 24: Complexity of a surgical intervention, from (Ergina, Cook et al. 2009)

Using the IDEAL framework

Perhaps due to this complexity, there has been a lack of accepted guidelines for generating valid evidence in surgery (Ergina, Cook et al. 2009). The Balliol Collaboration - developed out of the Balliol Colloquia, a series of meetings initially established to clarify methods related to the evaluation of surgical procedures - is a group of an invited international expert surgeons, methodologists, statisticians and epidemiologists from the UK, Europe and North America who met several times between 2007 and 2009, to explore the barriers to surgical research and to discuss and develop tools for surgical evaluation and innovation (Meakins 2007; Barkun, Aronson et al. 2009). The Balliol Collaboration constructed a paradigm to describe the development of evidence-based healthcare in surgery, the current standard for the development of medical knowledge (Barkun, Aronson et al. 2009), using a framework describing 5 stages of surgical innovation; Innovation, Development,

Exploration, Assessment and Long-term study (IDEAL) (Table 33) (Barkun, Aronson et al. 2009).

Table 33: Framework for a describing the surgical development process

Stage	Name	Brief Description
1	Innovation	First time procedure performed in humans, establishes proof of concept
2a	Development	Few surgeons performing procedure, safety data gathered
2b	Exploration	Many surgeons and more groups of patients, research databases established for safety outcomes
3	Assessment	Many surgeons and patients, clinically focused outcomes
4	Long-term study	Variations, long term outcomes and quality assurance

The Innovation stage is the first stage of the paradigm and includes the first time the new procedure is performed in humans, establishing a proof of concept. Very few surgeons perform the procedure at this time and publication of case reports is recommended, including both successful and non-successful procedures. The second stage is Development, as the procedure is refined, and safety and technical data begin to be reported. Exploration is the third stage, as the procedure is performed on many patients and the range of indications for use may expand. Safety outcomes are still the primary reportable measures at this stage, including the establishment of research databases, yet some data on clinical outcomes should be generated in small exploratory or feasibility controlled trials. Assessment of the procedure is the fourth stage, as use of the procedure expands to many surgeons, and it is only at this stage that the focus shifts to clinical outcomes. Finally, Long-term Study, the fifth stage, describes regional variations and audit of the procedure as data is collected in registries and routine databases, and reporting focuses on long term outcomes and quality assurance. (McCulloch, Altman et al. 2009)

Whilst the LSG itself is a reasonably established technique, which is endorsed by the Clinical Issues Committee of American Society for Metabolic and Bariatric Surgery (ASMBS Clinical Issues Committee 2009; ASMBS Clinical Issues Committee 2012), and has been reviewed in a Health Technology Assessment of weight loss surgery (Picot, Jones et al. 2009), its use in patients with CKD has not previously been studied. Therefore the IDEAL framework may be useful to address the ethical and practical issues of studying this procedure in obese patients with CKD. The case series reported in Chapter 3 aligns to the Stage 1 Innovation, as it established proof of concept of the procedure in a population in which it was not previously reported. Data on safety and efficacy were presented, including successful use of the procedure for weight loss and enabling kidney transplantation waitlisting, and some unexpected complications, such as loss of dialysis access and late-onset gastric leak (MacLaughlin, Hall et al. 2012). The prospective study of sleeve gastrectomy in obese patients undergoing haemodialysis presented in Chapter 4 is a Stage 2a Developmental study, and the randomised, controlled pilot study of LSG in obese patients with stages 3-4 CKD in Chapter 5 is an example of a Stage 2b Exploration study.

It can be difficult to define the point at which to move from an exploratory, or purely observational stage to a defined intervention trial, as if done too early, the standardisation required for a randomised or non-randomised trial may limit refinement of the technique, and if left too late, genuine equipoise may no longer be present (Ergina, Cook et al. 2009). Perhaps the most important consideration for determining when surgical research should move from an observational approach in the idea and development stages to small or pilot interventions in the exploration stage is the ethical examination of the risks and benefits profile of the procedure under study. Using the IDEAL framework, safety is the recommended primary outcome for all stage 2 studies (McCulloch, Altman et al. 2009). Indeed, in the case of weight loss surgery in obese patients with CKD, prior to the studies

in this thesis, there were no published reports specifically relating to LSG in patients with CKD. The IDEAL framework provides guidance on the appropriate study designs to focus on, to gather research data on the risk benefit profile of the procedure, prior to the expansion of practice and large interventional trials.

It has been suggested that, whilst the IDEAL framework supports the establishment of safety, efficacy, and effectiveness to reduce risks to patients, further consideration of broader ethical issues such as conflict of interest, informed consent, and improving public education and understanding of innovative surgery would enhance the recommendations (Johnson, Rogers et al. 2010). Conflict of interest between the surgeon as a researcher and the same surgeon as a clinician is a situation often present in surgical research. This conflict of interest presents a risk of influencing clinical judgement, which is not in the best interests of the patient (Johnson, Rogers et al. 2010). Addressing the potential conflict of interest in study design may be difficult, but nevertheless, should be acknowledged and declared if the risk is apparent. Explaining the risks of innovative surgery can be complex when little is known about the risks of innovative procedures, or about the risks of developing procedures in a novel population group. It is important that both known risks and the lack of information about possible or potential unknown risks, is adequately communicated to patients, since failing to communicate the lack of evidence to patients can impair the decision making process of informed consent (Johnson, Rogers et al. 2010). Improving public understanding of innovative surgical research is important to support the informed consent process. Greater public appreciation of the risks and potential harms associated with innovative treatment; together with the appreciation that novel procedures may not result in improved outcomes, is required to support the ethical adoption of innovative surgical research (Johnson, Rogers et al. 2010). Since this is likely to add another layer of complexity to the education and counselling required preoperatively,

improved education on healthcare and the process of research may reduce the burden of the decision-load on patients at the time a decision is required (Johnson, Rogers et al. 2010).

Using the IDEAL paradigm as a theoretical framework to underpin further research on surgical, or complex dietary and lifestyle, interventions for weight loss in obese patients with CKD, and to address the ethical issues raised in such interventions, further observational research is required before consideration can be given to the development of intervention trials in the assessment stage (Stage 3).

As the stages 3-4 CKD pilot study in chapter 6 had a primary outcome of efficacy, or clinical impact, rather than safety of the study procedure, it is placed at Stage 2b Exploration in the IDEAL framework. This trial may have been conducted prematurely, and perhaps research should have focused on further stage 2a safety research first, by establishing a research database in a retrospective or prospective observational study across several centres. This may have resulted in a study of a larger number of patients to better establish the safety of the procedure in obese patients with CKD, before commencing a pilot efficacy study. The studies in chapters 4 and 5 were conducted simultaneously in real time, therefore the risks of the procedure were unknown at the commencement of the exploratory study.

Establishing prospective studies and the London Renal Obesity Network

1 of the recommendations from the review of the study on haemodialysis patients presented in Chapter 4 was to gather together data on safety and efficacy of weight loss surgery in obese patients with CKD from other centres where the surgical procedures may also be taking place. We have since established the London Renal Obesity Network

(LonRON), as a pan-London interest group, consisting of Nephrologists, Bariatric Surgeons, Bariatric Physicians, Dietitians and Clinical Research Fellows. The initial aim of the network is sharing information and co-ordinating collection of safety and efficacy data from all bariatric surgery procedures in obese patients with CKD. 2 meetings have been held and retrospectively collected data on 70 patients is being collated and a joint renal-bariatric surgery protocol is being developed. This data collection and formation of a research database is further IDEAL Stage 2 Development and Exploration research. It is expected that the group will expand to a national network in due course, and will act as the research collaborative driving future studies on weight loss interventions in obese patients with CKD.

There is a need to establish a prospective research database, to further extend the work in Stage 2b Exploration, and the parameters for this have largely been established within the LonRON network. The next steps are to formalise the protocol and seek ethical approval, following the IDEAL recommendation (McCulloch, Altman et al. 2009), and seek funding to expand the database nationally. As the primary aim of this prospective study remains an examination of safety, with patient-centred and efficacy measures remaining secondary outcomes, no dilemma is presented about controlling aspects of the study which would need to be controlled in an intervention study, such as sample size, matched groups at baseline, and the robustness, validity and reliability of effectiveness outcome measures. This study may present an opportunity to refine clinical effectiveness outcomes. Furthermore, if such a study establishes that 1 or more of these procedures are likely to be safe, and the risks of the procedure/s can be presented to patients such that they can understand both the established short-term risks, but that long-term risks may still be unknown. Such a study would also generate data to enable calculation of the size of the

treatment effect, and the variation between patients, for planning a future controlled intervention trial.

Alongside such an observational study, further feasibility randomised controlled trials could be established, as well as further IDEAL Stage 2a safety and efficacy studies on other novel but non-surgical techniques (Barkun, Aronson et al. 2009), such as placement of intragastric balloon and/or endoluminal malabsorptive devices, by endoscopy, the results of which have not yet been reported in obese patients with CKD. It is recognised that studies of these devices will be as difficult to conduct as studies of weight loss surgery, in such that there are multiple components of the interventions to control to ensure the methodology is robust. Yet, as the procedures are temporary and reversible, patient recruitment may not be as difficult for a randomised trial study design, as compared with a study of a surgical weight loss procedure with randomised allocation to treatment.

Once the safety of 1 or more procedures is established in patients with CKD, if there is genuine equipoise over a study question explored in 1 or more further feasibility randomised controlled trials relating to a clinical outcome, a full randomised controlled trial with a primary clinical outcome may be justified. Despite the difficulties associated with standardisation of surgical techniques based on skill and adaptation to individual patients, and the challenges in designing such studies, the randomised controlled trial design remains the gold-standard study design to assess therapeutic interventions (Ergina, Cook et al. 2009).

There are several learning points to acknowledge from the study design presented in Chapter 5, which would need to be addressed and corrected in the design of a larger study. The use of a single study surgeon, even in a pilot study, may have been impractical, as the

results have no generalisability to other surgeons or centres. The number of secondary outcomes could be reduced to focus on clinical and patient-focused outcomes, such as changes in kidney function, proteinuria, metabolic syndrome components, insulin resistance and quality of life measures; and mechanistic outcome measures could be omitted. Defining the research question in an ideal randomised controlled trial also warrants greater consideration, as the choice of comparator is vitally important (Cook 2009). In the pilot trial presented in Chapter 5, the use of a lifestyle treatment comparator group did address the study question, and compared current standard care to the new procedure in question. However, as evident in the study in Chapter 5, recruitment to such a trial would be extremely difficult (Cook 2009), and is prone to a high attrition rate, as it is impossible to blind the patients to their treatment group, and techniques such as sham surgery or late randomisation several days before planned theatre are likely to be deemed unethical (Cook 2009; Ergina, Cook et al. 2009). The resulting groups, after attrition, may then not be matched at baseline as it is possible that patients likely to want surgery may be different to those likely to not want surgery, and allocation is no longer truly random. This could not be rectified using an intention-to-treat study design, as the level of cross-over between study groups may reduce the likelihood of a treatment effect being evident in either group. Another possible study design would be to randomise patients to surgery, or to a group waitlisted for surgery for 12 months; however, this prohibits any longer term follow up of kidney function and morbidity and mortality over time between groups.

These challenges, along with others, such as the learning curve evident in surgical practice with new procedures, funding of surgical studies and independent, blinded assessment of outcomes, have been highlighted in a recent review of challenges in the design and conduct of surgical randomised controlled trials (Cook 2009). The learning curve issue was addressed in the observational study in Chapter 4 and the pilot study in Chapter 5 by pre-

specifying a level of expertise obtained by performing at least fifty procedures previously; however, it became evident that in patients with end-stage kidney disease on haemodialysis treatment, that the condition of the vasculature was different in this patient group and the procedure required some minor alterations. With adequate resource, outcome assessors can be blinded to treatment allocation, even when it is not possible to blind patients or treatment providers.

3 recommendations have been made to foster the use of the randomised controlled trial methodology in surgical research: firstly, the most relevant and high impact innovations should be selected for randomised controlled trial research when the method of evaluation is ethical and feasible; secondly, a pragmatic approach to clinical research is useful and could be undertaken more often; and thirdly, the use of the randomised controlled trial method in exploratory research is recommended (Cook 2009) (and indeed may be more likely, given that the sample sizes for such research are likely to be smaller and equipoise is still genuinely evident).

If a randomised, controlled trial study design is truly impracticable, then one or more well-designed, high-quality prospective, large, cohort observational studies is recommended to identify treatment effects, patient-centred outcomes and cost-effectiveness (Ergina, Cook et al. 2009), and this may be the best approach to take in future studies of LSG, or other weight loss interventions, in obese patients with CKD, to determine the efficacy of the procedure for improving, or preventing decline, in kidney function.

A prospective, non-randomised, controlled, national study of LSG and other surgical procedures such as Roux-en-Y gastric bypass and adjustable gastric banding, with matching against other patients undergoing other weight loss procedures, such as lifestyle treatment,

with or without very low energy diets, with standardised methodology and rigorous attention to detail during data collection to limit missing data, is likely to be the most practicable and realistic study design to address the questions relating to clinical outcomes after LSG in obese patients with stages 3-5 CKD, including the nephron-protective effect of the procedure. Weaknesses in this study design are differences pre-treatment between groups and maintaining uniform treatment procedures in both surgical and non-surgical groups in a multi-site national study. The appointment of skilled researchers to maintain study integrity and perform outcome measurements in an observer-blinded manner, and skilled clinicians to deliver the interventions, together with surgeons with an established track record with the procedure/s in patients without CKD may address the second issue. Differences in groups pre-treatment is more difficult to address but may be surmountable if adequate information on potential patients is available prior to the study to enable matching across the country from a single electronic database. The establishment, and use, of such a database would also require ethical approval, but would also have benefits outwith the study.

The study would need both clinical and patient-reported outcomes (Ergina, Cook et al. 2009) such as health-related quality of life, and anxiety and depression scores, such as those in the studies presented in chapters 4 and 5. While interpretation of these scores may be difficult when groups are not well matched for these variables at baseline, it is difficult to control for this in an observational study design, and variables based on changes in these scores are recommended.

The primary outcome measure of kidney function with weight loss interventions in obese patients with CKD also needs to be considered. The use of the fingertip blood spot technique for iohexol clearance measurement of GFR was explored in the pilot feasibility

study presented in Chapter 5. This study revealed likely problems with this technique, as it is reliant on the correct timing and recording of the blood spots by the patients themselves. Furthermore, whilst iohexol measured GFR correlates highly with inulin clearance, the absolute gold standard measure (Brown and O'Reilly 1991), use of iohexol clearance in obese patients with CKD has not been compared to inulin clearance (Friedman, Strother et al. 2010), and use of patient-generated blood spot technique samples for iohexol clearance has not been validated in any patient population. Therefore, it is recommended that if the blood spot technique is to be used, it is performed by trained staff in a clinical setting, and that validation studies are carried out in obese patients with CKD prior to use in a large clinical trial. The use of serum cystatin C as a measure of kidney function is also currently being explored. Cystatin C is a basic protein produced in nucleated cells and removed by glomerular filtration and metabolised by the proximal tubules when kidney function is normal (Jesudason and Clifton 2012). Higher serum cystatin C is associated with renal dysfunction, and GFR can be estimated from the inverse of cystatin C concentrations or by using equations (Jesudason and Clifton 2012). However, there is still controversy in the current literature over the use of cystatin C measures of GFR in obese patients, particularly when measuring a change in kidney function after weight loss, which involves a change in body composition, due to an association with body weight, and/or an association with body fat (Naour, Fellahi et al. 2009; Friedman, Strother et al. 2010; Jesudason and Clifton 2012).

Therefore, there is much to be considered and examined before a large intervention trial examining the effect of weight loss interventions on kidney function in obese patients with CKD stages 3-4 is undertaken. Particular attention must be paid to establishing a valid and reliable measure of kidney function in obese patients that remains robust with changes in both fat and lean muscle mass over time, and the way in which the study designs will help

to answer the broader study question of "Does weight loss have an independent effect on kidney function in obese patients with CKD?".

Conducting interventional clinical research studies, even with small sample sizes, such as in this thesis, is difficult, due to the complex nature of interventions and external variations such as patient behaviour, availability of medication, surgical waiting times, and the time required to establish and then recruit to clinical studies with ethical and research and development department approvals on multiple study sites. In particular, studies of weight loss take a long time to complete, and run the risk of not achieving the intended weight loss, due to the presence of so many potential variations beyond the control of the researchers. Analysis of some novel parameters can be particularly time consuming, expensive and may not contribute significantly to the final study results, particularly when studies are ceased early due to safety concerns. Finally, in clinical interventions involving surgery, there is a demonstrated lack of research funding allocated to surgical academic training pathways, compared to that available and funded in medicine (Ergina, Cook et al. 2009), nursing, and allied health professions.

Whilst it is acknowledged that clinical intervention research is difficult, we have demonstrated that the risk for CKD increases as BMI increases in the UK population. Furthermore, a recent study from the United States indicated that 50% of overweight and obese patients with CKD in the NHANES 1999-2006 survey were seeking or undertaking weight loss treatments (Navaneethan, Kirwan et al. 2012). Therefore, there is a need to pursue this field of research despite the difficulties arising, and perhaps approach the problems with unique solutions based on the learning from the studies conducted in this thesis, and the recent literature on obesity and CKD.

Lifestyle interventions may delay mortality and cardiovascular morbidity, at least in the short-term; however a larger study with a longer follow-up period is recommended to substantiate this initial finding. Similarly, longer follow up of weight-loss outcomes for 2, 3, and up to 5-10 years after weight loss interventions is also warranted. Establishment of a national database of outcomes following weight loss intervention treatments in renal units across the UK would also support these types of studies, and the infrastructure of the Renal Registry is already in place to collect such data (United Kingdom Renal Registry). However the completeness of this database currently relies on the voluntary returns of these outcomes, and the quality of data is often dependent on the strengths and adaptability of the electronic medical records at individual hospital nephrology services.

New pharmacological treatments may also be developed, although no new weight loss drugs have been licenced since Rimonibant in 2006, which was subsequently withdrawn from sale in 2008 as the risk:benefit profile became unfavourable. The recent early cessation of the phase 3 BEACON trial of bardoxolone methyl, due to excess adverse events in the bardoxolone treatment group brings to a halt another line of investigation of a treatment, designed to slow CKD progression in patients with diabetes, but which also led to concurrent weight loss . Exenatide, a glucagon-like peptide-1 agonist, used to treat diabetes by enhancing insulin secretion from beta cells in the pancreas and suppressing glucagon, has been found to induce weight loss in patients with diabetes. A trial is currently underway to determine the effect of exenatide on weight loss in obese participants without diabetes . Other techniques are being investigated, such as Transcranial Direct Current Stimulation, in which a stimulus is delivered to the dorsolateral prefrontal cortex to mimic fullness, to determine the effect on food intake and weight loss .

It is likely that a combination of short-to medium-term clinical intervention studies to demonstrate the safety and efficacy of weight loss interventions in patients with CKD, together with large observational studies with outcomes such as kidney transplantation, cardiovascular event rates and mortality may be optimal to provide adequate insight into the utility of weight loss interventions in obese patients with CKD.

Conclusions

The key findings from this thesis are presented in Table 34.

Table 34: Key findings from the studies comprising Weight Loss Interventions in Obese Patients with Chronic Kidney Disease

Obesity is associated with an increased risk of CKD in a nationally representative sample of the population of England.
Patients participating in the Renal Weight Management Programme (diet, exercise and anti-obesity medication) may have a reduced risk of a combined event of all cause mortality, and cardiovascular morbidity, defined as myocardial infarction, stroke or hospitalisation for congestive heart failure, compared to patients who are referred to, but do not commence the programme.
Weight loss and fat mass loss achieved in the Renal Weight Management Programme is associated with a reduction in triglycerides.
Sleeve gastrectomy is an effective treatment for obesity and aids in meeting the criteria for kidney transplantation waitlisiting.
Sleeve gastrectomy may be associated with additional risks in patients with CKD, than had previously been reported in non-CKD populations, such as dehydration causing acute kidney injury, and loss of dialysis access.
Haemodialysis patients are likely to be at a greater risk for complications or adverse events after sleeve gastrectomy than patients with earlier stages of CKD and non-CKD patients.
Sleeve gastrectomy was associated with improvements in quality of life scores, and an increase in adiponectin, and decrease in insulin resistance compared to best medical care.
Sleeve gastrectomy was associated with a reduction in hyperfiltration at 12 months, compared to best medical care.
Estimated GFR consistently underestimated measured GFR in obese patients with CKD.
Large prospective observational studies in conjunction with smaller, well designed clinical trials of weight loss surgery are warranted, together with studies validating measures of kidney function in obese patients with CKD.

Obesity is a known risk factor for CKD, and this thesis reports evidence of this relationship for the first time in a UK nationally representative, randomly selected, population. Furthermore, the weight loss interventions presented in these studies provide initial evidence for beneficial treatment of obesity in patients with CKD. Compliance with lifestyle interventions was associated with improved blood pressure and a reduction in morbidity and mortality. This thesis also demonstrated the efficacy of LSG surgery for weight loss in patients with CKD for the first time, and showed improvements in kidney transplantation waitlisting in the case-series in Chapter 3, and improvements in adiponectin and quality of life measures with weight loss, and probable improvements in kidney function after weight loss surgery, in a small group of patients in the randomised controlled trial pilot study in Chapter 5. The studies also suggest that LSG surgery may be associated with an increased risk of complications in patients undergoing haemodialysis treatment, an effect borne out in other studies of weight loss surgery and all elective surgery (specifically in this patient group) published recently. Future research should focus on validation of a measure of kidney function in obese patients with CKD and on the development of a national research database of weight loss interventions in obese patients with CKD as a foundation to build upon for future interventional studies.

Presently, it is recommended that the selection of weight loss interventions should be individualised, based not only on an assessment of the risks and benefits of individual weight loss intervention procedures and the level of kidney function, but also in combination with thorough consideration of patient preferences, motivations, confidence, and previous experience with weight loss interventions.

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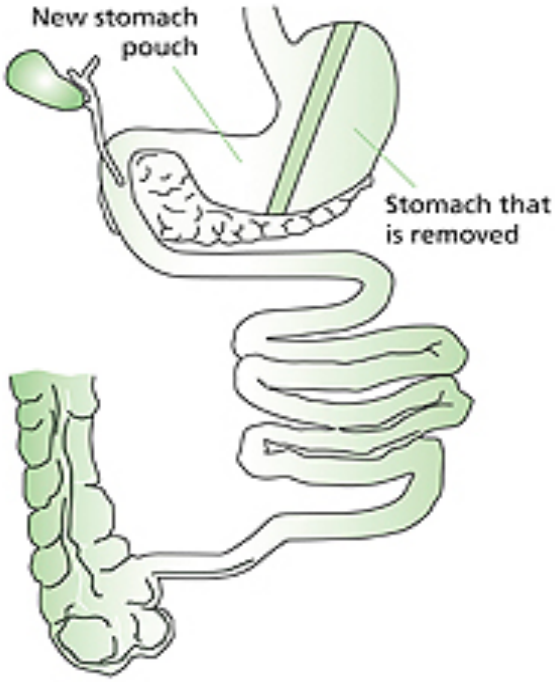
Appendices

King's College Hospital NHS
NHS Foundation Trust

Dietary information for Patients with Chronic Kidney Disease after Sleeve Gastrectomy



Dietitian Name: _____

Telephone Number: _____

What is a Sleeve Gastrectomy?
The stomach is made much smaller by cutting from top to bottom and leaving a banana shaped stomach along the inside curve. The stomach is reduced to one-third to one quarter of its usual size, but it still functions normally

The new stomach can only hold a few tablespoons of food after surgery, and eventually it will hold only about ½ to 1 cup. This will significantly reduce the amount of food you can eat.

The Eating Plan
After surgery you must stick to a strict eating plan to allow your new stomach to heal and to lose weight.

You should start with just liquids, followed by pureed and mashed foods and gradually move back to normal foods after the operation. To ensure you lose weight and keep it off, small meals are best in the long term.

Getting to your weight loss goal will still be difficult. Having surgery is only the first step, as it makes it harder, but not impossible to eat lots of calories. Greatest success is achieved with careful eating and by becoming more active.

What you can eat after your weight loss surgery will change as you recover from surgery and your stomach adjusts to its new size.

Stage	Time After Surgery	Eat/Drink
In hospital	2-5 days	Sips of clear fluids only
1	1-4 weeks	Fluids only
2	4-6 weeks	Puree and all fluids
3	6 weeks onwards	Soft foods and all fluids

First 2 to 5 days: Clear Fluids

In hospital you will have only clear sugar free liquids until after your dye test or gastrograffin test.

You can drink:

- water
- no added sugar squash
- clear soups
- tea and coffee without sugar
- unsweetened pure fruit juice

Notes:

- Try to sip fluids, so that you are drinking 80-100ml every hour that you are awake.
- **Use a Cup.**
- **Sipping fluids out of a bottle, sports bottle or through a straw may cause gas or bloating.**

1-4 weeks post op: Stage 1 – Fluids only

Once you have managed clear fluids and leave hospital, you may begin to have other liquids. Drinks that contain **protein MUST be included** to meet your needs for wound healing, organ function and to prevent loss of muscle.

Examples of fluids containing protein are:

- Semi Skimmed milk (you can add 2 tsp of skimmed milk powder to a glass of milk for extra protein)

  (You can use LactoFree® or soy milk with soy protein powder if you don't tolerate milk)

- Protein shakes: Ensure Plus, Fortisip Extra, Fortimel, Build Up® soups, Nepro
- Yogurt drinks and Smoothies
- Strained smooth soups e.g. cream of chicken or creamy vegetable with 2 tsp skim milk powder added

You will also need a chewable or crushed Multi-Vitamin and Mineral tablet twice a day. Sanatogen® Gold, Centrum® or Forceval® (prescribed by your GP) can be crushed between two spoons**.**
You may also need a special protein powder such as Renapro, Protifar or Forceval Protein which you can add to any drink 1-4 times per day, depending on your protein needs and your kidney function.

Sample meal plan for Stage 1: Fluids Only

Option 1	Option 2	Option 3
Breakfast 8am		
½ cup semi skimmed milk flavoured with instant coffee or espresso	**¼- ½ cup** of ready prepared smoothie	Banana smoothie (blend **¼- ½ cup** semi skimmed milk with **¼- ½** banana and 4 teaspoon of skimmed milk powder & honey)
Mid morning: 100 ml Ensure Plus, Fortisip Extra, Fortimel, Nepro		
Lunch 12pm		
½ cup-a-soup (strained) with 4 tsp skimmed milk powder added	½ cup semi skimmed milk with 4 tsp skimmed milk powder, flavoured with drinking chocolate/nesquik	**¼- ½ cup** of liquid yoghurt (eg: Danone® Actimel Strawberry 0.1% Fat)
Mid afternoon: 100 ml Ensure Plus, Fortisip Extra, Fortimel, Nepro		
Dinner 6pm		
Strawberry smoothie (blend **¼- ½ cup** semi skimmed milk with **¼ cup** berries and 2 teaspoon of skimmed milk powder)	100 ml Ensure Plus, Fortisip Extra, Fortimel or Nepro	**½ cup-a-soup** (strained) with 4 tsp skimmed milk powder added
Snack 8pm		
100 ml Ensure Plus, Fortisip Extra or Fortimel	**¼- ½ cup** semi skimmed milk + 4 tsp skimmed milk + **2tsp** drinking chocolate	**¼- ½ cup** of smoothie or fruit juice

4 -6 weeks post op: Stage 2 - Puree diet

- Food at this stage should fall off the spoon and be smooth with no lumps.

- All freshly prepared low fat low sugar foods can be eaten as long as they are put into a blender and the final consistency is puree.

- Liquid will need to be added when blending foods (eg: fruit juice when blending fruits, gravies, stock or soup when blending meats, beans and vegetables).

- On some days you may tolerate foods well, but other days you may not. Retry foods you don't tolerate a few days later.

- Sip liquid between meals. Do not drink during meals. Try to drink _____cups of water, sugar free squash, skim milk, clear soup, coffee or tea daily

- Continue to take a Multi-Vitamin and Mineral Supplement: eg: Centrum®, Sanatogen® Gold or Forceval® once a day (can be prescribed by your GP)

- If you need a "ready meal" try any meat, fish or chicken stage 1 baby meal. They are the perfect portion size too.

- After a couple of weeks you can once you tolerate sloppy pureed foods, you can begin to include mashed consistency foods like:
  - thoroughly mashed tuna salad/moist fish/eggs with added extra light mayonnaise
  - well mashed ripe bananas, cooked/canned apples, pears, apricots

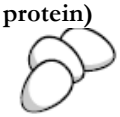
Continue to sip 100-150 ml fluid every hour

throughout the day.

You will need to drink at least <u>1500-2000 ml</u> of

water/tea/coffee/squash/herbal tea/clear soup

Stage 2: Puree diet (from approx weeks 4 to 6 post op)

Food Group	Serving size & serves/day	Food Choices
Pasta, bread, cereal and rice	*1-2 serving per day* 1 serving = ¼ cup	Porridge, readybrek, mashed up Weetabix® or Oatibix®
Fruit 	*2 servings per day* 1 serving = ¼ cup	Unsweetened apple sauce, any fruit puree, mashed ripe banana
Vegetables 	*2 servings per day* 1 serving = ¼ cup	Well cooked soft vegetables (such as courgettes, broccoli, cauliflower, swede) blended or mashed with a fork with gravy or vegetable stock added to achieve correct consistency Smooth blended soups -minestrone, cream of tomato, country vegetable – all well blended without lumps
Meat, Poultry, Fish, Beans, Eggs **(high protein)** 	*3-4 servings per day* 1 serving = ¼ cup	Chopped up soft poached eggs or scrambled eggs. Blended moist meat, chicken and flaked fish cooked very soft and moist. Add water, stock, or milk when blending to a smooth puree.
Milk, cheese, yoghurt **(high protein)** 	*3 servings per day* 1 serving = ¼ cup*	Low fat cottage cheese or ricotta cheese (*1 serve = ½ cup for these); reduced fat cheddar cheese (melted); Custard made without sugar, quark, fat free, sugar free yogurt
Other	*1-2 servings per day* 1 serving = ¼ cup	Sugar free jelly, low calorie hot chocolate mixes (eg: Options®, Cadburys® Highlights).

Sample Meal Plan for Stage 2:

Option 1	Option 2	Option 3
Breakfast 8am		
¼ cup Porridge/1 Weetabix®/**¼ cup** Ready Brek® made with **½ cup** milk	**¼ cup** diet/plain yoghurt or fromage frais **¼ cup** pureed fruit	**1** scrambled or poached egg ¼ cup pureed fruit or juice
Mid morning: 100ml Ensure Plus, Fortisip Extra, Fortimel, Nepro		
Lunch 12pm		
¼ cup egg salad (chopped up boiled egg with low fat mayo add very finely chopped fresh chives) **¼ - ½ cup** blended chicken soup	**¼ - ½ cup** canned celery soup **¼- ½ cup** flaked tuna mixed with low fat mayo ¼ cup pureed fruit	**¼ - ½ cup** low fat cottage cheese **¼ cup** unsweetened apple sauce with cinnamon or pureed broccoli or peas
Dinner 7pm		
¼ cup tuna with low fat mayo **½ cup** blended vegetable soup ¼ cup pureed fruit	**¼ cup** meat or chicken pureed with gravy **1** egg sized potato mashed **¼ cup** pureed veg	**¼ cup** white fish pureed with milk **1** egg sized potato mashed with milk, **¼ cup** pureed veg
Mid morning: 100ml Ensure Plus, Fortisip Extra, Fortimel, Nepro		
Snack		
¼ cup pureed canned fruit	**½ cup** skimmed milk **2tsp** low calorie hot chocolate	**¼ cup** diet/plain yoghurt with ¼ cup sugar free jelly

6 weeks post op: Stage 3 - soft diet

You can now begin to add:

- tofu, fish and seafood, thinly sliced turkey, ham or other lean cold meats
- slices of low fat cheese
- unsweetened canned or cooked fruit,
- potatoes, butternut squash
- unsweetened cereal (ie. Cornflakes®, Rice Krispies®, Cheerios®) with skimmed milk
- crisp toast and crackers, well cooked pasta
- beans and peas, and lean, moist minced chicken and beef

As soon as you feel pressure in the centre of your abdomen stop eating and drinking. If you feel nauseous stop eating. One extra mouthful of food after these early signals can lead to pain, discomfort and vomiting.

Eat slowly and chew thoroughly- at least 25 times until food reaches a puree texture. It should take at least ½ hour for each meal.

Adult Multi-Vitamin and Mineral Supplement: Centrum®, Sanatogen® Gold or Forceval® (can be prescribed by your GP), **once a day**.

High protein milk drink – add 4 tsps of skimmed milk powder to ½ cup of skimmed milk and mix well

Sample Meal Plan Stage 3

Breakfast 8am		
Option 1	Option 2	Option 3
¼ cup Special K® **½ cup** skimmed milk 1 small banana	**1**Weetabix® **½ cup skim milk** **¼ - ½ cup** frozen berries	**1** Egg scrambled **30g** reduced fat cheddar + 1/2 grilled tomato
Mid morning: **high protein milk drink**		
Lunch 12pm		
Option 1	Option 2	Option 3
1 slice granary bread, toasted **30g** reduced fat cheese **1** tomato, sliced	**1-2** Ryvitas® **or** **3-4** water crackers **¼ cup** reduced fat hummus mixed salad leaves **30g** ham	**1** Small boiled potato (don't eat the skin) **¼ cup** baked beans & **30g** reduced fat cheese
Dinner 7pm		
Option 1	Option 2	Option 3
¼ cup minced meat, cook with garlic and herbs **¼ - ½ cup** carrots and cauliflower **2 e**gg sized potatoes mashed	**½ cup** pasta**, ¼ to ½ cup** reduced fat ricotta cheese **½ cup** boiled veg, mashed	**¼ cup** fish, with low fat white sauce **¼- ½ cup s**weet potato, mashed **¼- ½ cup** aubergine and courgette with italian dried herbs
Snack		
¼ cup sugar free jelly + **¼ cup** fat free, sugar free yoghurt	**¼ cup** Canned fruit with **¼ - ½ cup** low fat, low sugar custard	**½ cup** skimmed milk **2tsp** low calorie hot chocolate

2 Months post-op: Diced poultry (no skin), vegetable burgers, soft cooked vegetables, soft fruits (watermelon, honeydew, peaches, plums)

3 Months post-op: Rice, soft bread, lean and moist meat and poultry

4 Months post-op: crunchy fruits and vegetables including salads

Lifelong Nutrition Habits

To keep the weight off you will need to maintain a healthy eating plan for the rest of your life.

Include protein and fruit and/or vegetables in each meal every day to keep meals high in protein and low in calories. Choose:

- fish, chicken, turkey, lean meat, eggs, tofu, skimmed milk, low fat yoghurt for protein
- fresh, frozen, or canned fruits and vegetables (without syrup, juice, added fat or sauces). Eat 2 pieces of fruit and 2 different vegetables every day – for fibre, vitamins and minerals.

Limit starchy foods as these are the easiest to over eat and may stretch you new stomach. Stick to 3 small serves of starchy foods each day. One serving = a slice of wholegrain bread, ½ cup cereal, ½ potato; ½ cup of cooked rice or pasta

Continue to eat three regular meals and **one** snack each day. If you snack throughout the day you will probably over eat and your weight loss will slow down or stop.
Liquids should always be calorie free. Always choose water, no added sugar squash, tea, coffee or skimmed milk.

Adult Multi-Vitamin and Mineral Supplement: eg: Centrum®, Sanotagen® Gold or Forceval® (can be prescribed by your GP), **once a day**.

Remember that food preparation is important – avoid fried foods and roasting with added fats. Choose to grill, steam, bake or boil your meals. Remove all visible fat and skin from meats before cooking. If you do fry, use a non-stick pan with an oil spray or a tablespoon of water in the fry pan to stop food sticking to the pan.

Always avoid these high calorie foods and drinks:

- squash, fizzy drinks, milkshakes, lucozade
- whipped cream, double cream, ice cream, condensed milk, evaporated milk
- butter, lemon curd, chocolate spread
- regular cheese and hard cheeses
- nuts, crisps, chips, dried fruit, bombay mix
- chocolate, sweets, cake, muffins and biscuits
- breakfast cereals with sugar or chocolate coating
- muesli bars/flap jacks/cereal bars with chocolate
- deep fried foods, pastries, palm oil
- creamy or oil based salad dressings
- sugar, glucose, invert syrup, high fructose corn syrup, golden syrup, treacle

Alternative Meal Plan for Stage 1 – Fluids only

Time	*Fluid and amount*

For more information on weight loss surgery, try these UK websites

British Obesity Surgery Patient Association:

http://bospa.org.uk/Information.aspx?Page=13

Obesity Surgery Advice:

Appendix B - SF-36 Quality of Life Questionnaire and Hospital Anxiety and Depression Scale

Date of assessment |_|_| |_|_| |_|_|
dd mm yy

SF-36 HEALTH SURVEY

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **half a mile**	1	2	3
i. Walking **one hundred yards**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

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5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

No bodily pain 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Hospital Anxiety and Depression Scale (HADS)

Choose one response from the four given for each statement, to describe your feelings today. The response should be the first one that appears to apply and you should not think for too long about your answers.

A	**I feel tense or 'wound up':**	
	Most of the time	**3**
	A lot of the time	**2**
	From time to time, occasionally	**1**
	Not at all	**0**

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Thank you

Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.	
0-7 = Normal	
8-10 = Borderline abnormal	
11-21 = Abnormal	
Total for A =	Total for D =

Reference: *Zigmond and Snaith (1983)*

Patient ID: CKD 34 ☐☐☐☐☐☐☐**B/3/6/9/12** (circle)

Score entered onto database ☐

Date _____ Signature _____

Appendix C - Information for Participants and Consent Form for Weight loss surgery for obesity in haemodialysis patients (Chapter 4)

King's College Hospital NHS Foundation Trust
Guy's and St Thomas' NHS Foundation Trust
St George's Healthcare NHS Trust
Epsom and St Helier University Hospitals NHS Trust

Information for Participants

Research Ethics Committee Reference Number: 10/H0716/55

Study Title: Weight loss surgery for obesity in haemodialysis patients

We would like to invite you to participate in this original research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take some time to read and consider the following information carefully and discuss it with friends, relatives or your doctor if you want to. Ask us if there is anything that is not clear, or if you would like more information.

Research Aim - What we would like to find out

This study's purpose is to determine if keyhole surgery for weight loss surgery using the sleeve gastrectomy operation is effective for weight loss in haemodialysis patients with a body mass index (BMI) greater than 35 kg/m2. The research will also monitor changes in blood pressure, blood fats, quality of life and the side effects of the operation in haemodialysis patients.

We would like to study patients who wish to have weight loss surgery and also those who wish to continue with their current medical care. If you were to participate, you can choose to have keyhole surgery to permanently remove two-thirds of your stomach in a procedure called a sleeve gastrectomy, or choose to continue with your current treatment. Both groups will have follow-up appointments every 3 months for 1 year.

Background Information – What we already know

We know that obesity and chronic kidney disease both increase the risk of heart and blood vessel disease, and that patients on dialysis have a very high risk of dying from heart problems. Obesity also stops patients from being able to get on to the kidney transplantation waiting list.

Weight loss surgery is well established as the most effective method of achieving and sustaining long term, significant weight loss in people with normal kidneys. On average, patients lose 30% of their body weight within 1 year. It is not without risks though, and

because not many patients on dialysis have had this type of surgery, we do not know all the risks yet. However, the bigger you are, the more risky any operation will be.

Some weight loss operations may not be good for patients with kidney disease. Both the gastric bypass and gastric band may cause complications, particularly after a kidney transplant. This research study will measure the amount of weight loss achievable and monitor patients for possible, but rare, side effects.

The 2 treatment options
If you volunteer to participate in this research you can choose to join the surgery group or the best medical care (no surgery) group.

Best Medical Care
You will continue to receive your current level of medical care from your kidney doctor and the dialysis team. You will also be able to access personalised dietary education and support for weight loss from the renal dietitian working in the study.

Weight Loss Surgery
If you choose to have weight loss surgery, you will continue with your current medical care form the kidney doctor and the dialysis team. You will also have an operation called a laparoscopic sleeve gastrectomy.

Sleeve gastrectomy is a relatively new procedure for weight loss surgery and so far, it has been seen as safe and effective. However there is no information on its success and safety for patients on dialysis.

It is a permanent operation which reduces the size of the stomach. After a general anaesthetic to put the patient to sleep, the surgeon will insert a laparoscope (thin, tube like instrument with a camera to see inside the body) and other slender surgical instruments into the abdominal cavity, through very small surgical cuts in the abdomen. The surgeon will then remove about 2/3 of the stomach using a cutting and stapling device after disconnecting the blood supply. The stomach will function as normal, but the reduced size means patients should feel fuller, sooner, so eat less. The level of the hunger hormone, Ghrelin, which is produced in the stomach, will be reduced, and this should reduce appetite.

The surgeon may also take a small sample of your fat tissue whilst he is performing the surgery. This tissue will be frozen and stored for later analysis related to this research.

The risks associated with the sleeve gastrectomy are the same as those for any other major abdominal procedure and include haemorrhage (bleeding), leaks from staple lines, anaesthetic and drug reactions, deep vein thrombosis (DVT), pulmonary embolus (blood clots on the lung), infection, marginal ulcer, and lung problems. Overall the risk for any of these early complications varies between 3-7% (or 3-7 times in 100) and with an experienced surgeon the risk of death during a sleeve gastrectomy is very low – around 0.1-0.5% (or 1 in 500 to 1 in 1000). There is also a small chance that weight loss will be less than expected. Weight re-gain may occur in 2-3 years if a low fat, low sugar eating plan is not followed in the long term.

After the operation, patients are encouraged to perform exercises to improve lung function and swallow a special fluid to check for leaks in the new stomach, as there is a long staple line in the stomach afterwards. Most patients will stay in hospital for 2-5 days.

Collecting Information
The study team will collect information about patients throughout the study. All data will have patient identifiable information removed (name, address, date of birth) before it is coded and entered into the research database. A separate code breaker file will be kept securely in the study office, to identify patients when new data is added.

The results of the study will be analysed and a report will be written, which may be published in a science journal within two years. If the study finds out something significant the study team may contact the media, and a summary of the results may be published in newspapers. No patient who takes part in the study will be identified in any way in the results.

Telling your GP
The study team will write to your GP to let them know you are participating in this study.

Before you decide to join the study
Patients who are interested in participating in the study will discuss the study and the additional appointments involved with the study dietitian and their kidney doctor. If you know you do not want to have surgery but are willing to participate in the study, you will be invited to an appointment for the baseline assessment.
If you would like to consider having surgery you will be invited to a pre-assessment appointment with the weight loss surgeon and dietitian. The surgeon will check your medical history and answer all the questions you have about the risks and benefits of surgery. The dietitian will give you information about eating after surgery, including a phase of up to 6 months with fluids only and progression to texture modified meals.

Tests and measurements during the study
The study involves 5 study visits over 1 year, plus the pre-surgery assessment appointment. Each study visit will involve monitoring of dietary intake and physical activity, fasting blood tests and other measurements. Each visit will last about 1 hour and where possible, will be on the same day as your dialysis.
Adverse Events and Complications
For the length of the study, any new medical problems or any admissions to hospital will be recorded for all patients. This will help to determine what side effects or complications, if any, may be related to the weight loss operation in dialysis patients. All information will be strictly confidential and none of this information will be able to be traced back to any individual patient enrolled in the study.
Bioelectrical Impedance Analysis
This is a device similar to a pair of scales but instead of measuring only your weight it also measures your body water, muscle and fat levels. You will need to remove your socks and shoes. An undetectable current passes from underneath the feet around the body, measuring the amount of water in the body. Estimates of body fat and lean tissue are then determined. Patients must not eat or drink anything for 2 hours before the test is done. The measurement will be made at baseline and every 3 months up to 1 year.

Blood Tests
Fasting blood samples
The study will involve providing an early morning fasting blood sample at the beginning and every 3 months up to 1 year. Patients will have to attend the hospital in the morning after not eating for 6-12 hours.

Approximately 40 ml of blood will be taken on each occasion, usually from the dialysis machine. If the blood has to be taken directly from you, there is a possibility that some bruising may occur at the site after the sample has been taken.

Some of this blood will be analysed for this study and some samples from this study may be used in future research, relating to this study only, when new techniques are available for measuring previously unknown risk markers.

Blood Pressure
Blood pressure will be measured whilst you are on dialysis and an average of the values calculated over a two week period. The measurement will be made at baseline and every 3 months up to 1 year.

Blood vessel stiffness (Pulse Wave Velocity)
Pulse wave velocity measures the time it takes for a pulse or wave to travel through your blood vessels. One pressure sensor will be put on your neck and another on your thigh whilst you lie flat and rest for 10 minutes. After the rest period, the time between your pulse detected at your neck and your thigh is measured and your blood pressure will be taken several times. The measurement will be made at baseline and every 3 months up to 1 year.

Food and Activity Diaries
Patients will be required to keep a detailed written record of all food and drink consumed and all activity undertaken for a 3 day period, including 1 weekend day, at baseline and every 3 months, up to 1 year. The diary will be provided by the study team and can be returned in a pre-stamped pre-addressed envelope provided.

Nutrition Assessment (SGA)
This test is used to monitor nutritional status and to detect poor nutrition in patients, and is used as part of a standard nutrition assessment in dialysis patients. It involves answering some general questions about weight change, activity, food intake and gastro-intestinal symptoms, and having a health professional examine your head, shoulders, arms and legs for muscle wasting. You may have to remove some of your clothing so the health professional can see your shoulders, arms, knees and ankles. The measurement will be made at baseline and every 3 months up to 1 year.

Questionnaires
Patients will be asked to complete two questionnaires. The Renal Quality of Life questionnaire is 12 pre-set questions relating to your own perception of your quality of life. The Hospital Anxiety and Depression Score questionnaire is set of 14 multiple choice questions. The questionnaires will be completed at baseline and every 3 months up to 1 year.

Weight, waist and hip circumferences
Body weight will be measured by standing on digital weighing scales in light clothing. Waist and hip circumferences will be measured over light clothing with a soft tape measure. These measurements will be made at baseline and every 3 months up to 1 year.

It is up to you to decide whether to take part or not
It is up to you to decide whether or not to take part. If you do decide to take part, please keep this information sheet. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

Consent to participate
If you decide to join this study you will be asked to sign a consent form. The consent form will ask that you agree to participate in this study in the treatment arm that you have chosen. The consent form will also ask that you allow your blood, urine and tissue samples to be kept for future research related to this study only.

Who is organising and funding the research?
The study is organised and funded by King's College London and King's College Hospital. Your Doctor, Dietitian and the lead investigator are not being paid to recruit you to this study.
Who has reviewed the study?
This study has been reviewed by the King's College Hospital Research and Development Committee and approved by the Central London Research Ethics Committee 3.

Can I speak to anyone not involved in the study about participating in research?
If you are thinking about participating, and you would like to speak to someone not directly involved with the study, you can contact PALS (the patient advice and liaison service), or the renal anaemia research team to get independent advice about participating in research.

PALS
King's College Hospital tel 020 3299 9000 ext 3601 or visit them on the ground floor, Hambledon Wing 9am to 6pm Monday to Friday
Guy's and St Thomas' Hospital tel 020 7188 8801 or visit them on the second floor, Southwark Wing (Thomas Guy House) 12pm to 3pm Monday to Friday
St George's Hospital tel 020 8725 2453 or visit them in the main corridor between Grosvenor and Lanesborough Wing near the lift foyer 9am to 5pm Monday to Friday
St Helier Hospital tel 020 8296 2508 or visit them on the ground floor next to reception at the main entrance 9am to 5pm Monday to Friday

Or log on to the PALS website
http://www.pals.nhs.uk/

Number of visits
Overall, there are up to 5 study visits to the hospital over 1 year (plus the surgery pre-assessment for those who choose have weight loss surgery) if you participate in the research.

You can use this table to write in the dates of your appointments, if you decide to take part.

Month	Study visit	Date	Best Medical Care	Weight Loss Surgery
-3			-	assessment for surgery
0	1		baseline (beginning) tests and measurements	baseline (beginning) tests and measurements and weight loss surgery operation
3	2		3 month tests	3 month tests
6	3		6 month tests	6 month tests
9	4		9 month tests	9 month tests
12	5		12 month tests	12 month tests

Study Team

Dr Iain Macdougall
Consultant Nephrologist
King's College Hospital NHS Foundation Trust

Mr Ameet Patel
Consultant Surgeon
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Dr Mysore Phanish
Consultant Nephrologist
St Helier Hospital NHS Trust

Dr Iain McPhee
Consultant Nephrologist
St George's Hospital NHS Trust

Professor Tom Sanders
Head of Nutritional Sciences Division
King's College London

Details of local contact
If you require any more information or have any questions, please contact the study co-ordinator:
Helen MacLaughlin
Renal Dietitian
King's College Hospital
020 7848 0431
helen.maclaughlin@ nhs.net

Epsom and St Helier University Hospitals NHS Trust

Guy's and St Thomas' NHS Foundation Trust | St George's Healthcare NHS Trust | King's College Hospital NHS Foundation Trust

Weight loss surgery for obesity in haemodialysis patients

PARTICIPANT CONSENT FORM

REC Reference Number: 10/H0716/55
Patient identification number for this trial:

Study title: A prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in obese patients on haemodialysis.

Lead Investigators/Researchers:
Helen MacLaughlin – Lead Renal Dietitian King's College Hospital & PhD student King's College London
Dr Iain Macdougall – Consultant Nephrologist King's College Hospital
Mr Ameet Patel – Consultant Surgeon King's College Hospital
Dr Paramit Chowdhury – Consultant Nephrologist Guy's Hospital
Dr Mysore Phanish – Consultant Nephrologist St Helier Hospital
Dr Iain McPhee – Consultant Nephrologist St George's Hospital
Professor Tom Sanders – Head of Nutritional Sciences Division King's College London

Please initial the boxes

1. I confirm that I have read and understood the information sheet (version 2.0) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that the risks and benefits of participating in the study have been explained to me in a way that I understood. ☐
3. I confirm that the risks and benefits of the individual procedures in the study have been explained to me in a way that I understood. ☐
4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐
5. I understand that responsible individuals from King's College Hospital may look at relevant sections of my medical history. I give permission for these individuals to have access to my records. ☐
6. I agree that the researchers may contact my GP to inform them of my participation in this study. ☐

7. I agree to have the study measurements completed and have blood samples taken for use in this study and to also have samples stored for later research related to this study only. ☐

For Weight Loss Surgery Treatment only

8. I agree to take part in the above study, and I understand that I will undergo a permanent surgical procedure called a laparoscopic sleeve gastrectomy which will require life long alterations in my eating habits in order to lose weight and maintain weight loss over time. ☐

9. I agree to have a fat tissue biopsy taken at the time of surgery and for the tissue to be stored for later research related to this study only. ☐

Name of Patient_____Date _____
Patient's Signature_____

Name of Researcher _____ Date _____
Researcher's Signature _____

Appendix D - Instructions for Recruitment, Pre-assessment Data Collection and Monitoring

King's College Hospital NHS
NHS Foundation Trust

The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with chronic kidney disease: a randomised controlled pilot study

REC Reference Number: 09/H0806/69 and R&D Reference Number: KCH 1639

and

A prospective cohort study of laparoscopic sleeve gastrectomy for weight loss in obese patients on haemodialysis: pilot study

REC Reference Number: 10/H0716/55 and R&D Reference Number KCH 11-014

Detailed methodology for Recruitment, Pre-assessment, Data Collection and Monitoring

Recruitment

Patients will be recruited through existing outpatient clinics linked with the 3 study sites. Referrals will be made to the study co-ordinator or renal dietitian by the treating clinic team for eligible patients who agreed to be referred for weight management treatment. All referred patients will be contacted by the study co-ordinator by telephone or in person and sent/given written information on the study, with a follow up telephone call 1-2 weeks later. If the patient is interested in the study they will be invited to attend the pre-surgery assessment or for the HD study non surgical arm, pre-study assessment.

Pre-surgery assessment

Patient attends the pre-assessment appointment with Surgeon and Dietitian to determine legibility for surgery and allow the patient find out further information about the study and ask questions to satisfy the terms of informed consent.

The patient will see the renal dietitian initially, who will explain the current treatment option of weight management clinic, including the expectations of the patient and treating team, optional medication use, programme results and effect on kidney function with level of weight loss achieved. The dietitian will also explain that the study is exploring an additional form of treatment for weight loss, which is effective for weight loss in the general population but relatively new in patients with chronic kidney disease.

The patient will then see the surgeon and dietitian together:

a. Surgeon asks patient whether they are willing to have an operation to lose weight, discusses history of being overweight and attempts at weight loss, records detailed medical history (includes identification of sleep apnoea risk), surgical history, family history of chronic diseases, bowel diseases and inheritable conditions, especially those relating to bleeding or clotting, reasons patient wants to lose weight and what the patient expects from weight loss surgery
b. Surgeon conducts abdominal examination
c. Surgeon makes assessment about suitability for weight loss surgery
d. If patient suitable for weight loss surgery the consultation continues, Surgeon explains the research study, including the weight loss operation involved (laparoscopic sleeve gastrectomy), process of randomisation, giving informed consent, freedom to withdraw, and the study outcomes and how these are relevant to the patient
e. Dietitian records dieting history and eating habits, including any out of control experiences to determine potential eating behaviour barriers to weight loss (can use Binge Eating Scale* if appropriate)
f. Dietitian explains the dietary and lifestyle considerations for each treatment arm including low fat calorie reduced diet for lifestyle modification and texture modified progression and lifelong altered portion size for surgical treatment arm
g. Dietitian explains level of likely weight loss in each treatment arm, number of appointments in each treatment arm and tests involved
h. Discussion about the study with patient and answer all patient questions
i. If patient willing to participate, obtain informed consent to participate in randomised controlled trial
j. Refer to sleep clinic or other services as required
k. If participating in trial, patient informed of randomisation process and to await results of randomisation allocation
l. If patient does not wish to be considered for the trial, surgeon will continue appointment to determine course of treatment

*BES – Binge Eating Scale

Give patient the questionnaire and ask them to complete according to the instructions on the questionnaire. You may read out the instructions.

To score the BES, add up the scoring weights in parentheses. Scores of 16 or less indicated no binge eating problem identified, scores of 17-26 indicate mild to moderate binge eating problem identified, and scores of 27 or more indicate severe binge eating problem identified. Patients scoring 17 or more should undergo treatment for Binge Eating Disorder using CBT techniques, prior to proceeding further in the study.

Eating Habits Checklist

Instructions. Below are groups of numbered statements. For each group, read all of the statements and mark on this sheet the one that best describes the way you feel about the problems you have controlling your eating behaviour.

#1

(0) 1. I don't feel self-conscious about my weight or body size when I am with others.
(0) 2. I feel concerned about how I look to others, but it normally does not make me feel disappointed with myself.
(1) 3. I do get self-conscious about my appearance and weight which makes me feel disappointed in myself.
(3) 4. I feel very self-conscious about my weight and frequently, I feel intense shame and disgust for myself. I try and avoid social contacts because of my self-consciousness.

#2

(0) 1. I don't have any difficulty eating slowly in the proper manner.
(1) 2. Although I seem to "gobble down" foods, I don't end up feeling stuffed because of eating too much.
(2) 3. At times, I tend to eat quickly and then, I feel uncomfortably full afterwards.
(3) 4. I have the habit of bolting down my food, without really chewing it. When this happens I usually feel uncomfortably stuffed because I've eaten too much.

#3

(0) 1. I feel capable to control my eating urges when I want to.
(1) 2. I feel like I have failed to control my eating more than the average person.
(3) 3. I feel utterly helpless when it comes to feeling in control of my eating urges.
(3) 4. Because I feel so helpless about controlling my eating I have become very desperate about trying to get in control.

#4

(0) 1. I don't have the habit of eating when I'm bored.
(0) 2. I sometimes eat when I'm bored, but often I'm able to "get busy" and get my mind off food.
(0) 3. I have a regular habit of eating when I'm bored, but occasionally, I can use some other activity to get my mind off eating.
(2) 4. I have a strong habit of eating when I'm bored. Nothing seems to help me break the habit.

#5

(0) 1. I'm usually physically hungry when I eat something.
(1) 2. Occasionally, I eat something on impulse even though I really am not hungry.
(2) 3. I have a regular habit of eating foods, that I might not really enjoy, to satisfy a hungry feeling even though physically, I don't need the food.
(3) 4. Even though I'm not physically hungry, I get a hungry feeling in my mouth that only seems to be satisfied when I eat a food, like a sandwich, that fills my mouth. Sometimes, when I eat food to satisfy my mouth hunger, I then spit the food out so I won't gain weight.

#6

(0) 1. I don't feel any guilt or self-hate when I overeat.
(1) 2. After I overeat, occasionally I feel guilt or self-hate.
(3) 3. Almost all the time I experience strong guilt or self-hate after I overeat.

#7

(0) 1. I don't lose total control of my eating when dieting even after periods when I overeat.
(2) 2. Sometimes when I eat a "forbidden food" on a diet, I feel like I "blew it" and eat even more.
(3) 3. Frequently, I have the habit of saying to myself, "I've blown it now, why not go all the way" when I overeat on a diet. When that happens I eat even more.
(3) 4. I have a regular habit of starting strict diets for myself, but I break the diets by going on an eating binge. My life seems to be either a "feast" or "famine".

#8

(0) 1. I rarely eat so much food that I feel uncomfortably stuffed afterwards.
(1) 2. Usually about once a month, I eat such a quantity of food, I end up feeling very stuffed.
(2) 3. I have regular periods during the month when I eat large amount of food, either at mealtime or at snacks.
(3) 4. I eat so much food that I regularly feel quite uncomfortable after eating and sometimes a bit nauseous.

#9

(0) 1. My level of calorie intake does not go up very high or down very low on a regular basis.
(1) 2. Sometimes after I overeat, I will try to reduce my calorie intake to almost nothing to compensate for the excess calories I've eaten.
(2) 3. I have a regular habit of overeating during the night. It seems that my routine is not to be hungry in the morning but overeat in the evening.

(3) 4. In my adult years, I have had week-long periods where I practically starve myself. This follows periods when I overeat. It seems I live a life of either "feast or famine".

#10

(0) 1. I usually am able to stop eating when I want to. I know when "enough is enough".
(1) 2. Every so often, I experience a compulsion to eat which I can't seem to control.
(2) 3. Frequently, I experience strong urges to eat which I seem unable to control, but at other times I can control my eating urges.
(3) 4. I feel incapable of controlling urges to eat. I have a fear of not being able to stop eating voluntarily.

#11

(0) 1. I don't have any problem stopping eating when I feel full.
(1) 2. I usually can stop eating when I feel full but occasionally overeat leaving me feeling uncomfortably stuffed.
(2) 3. I have a problem stopping eating once I start and usually I feel uncomfortably stuffed after I eat a meal.
(3) 4. Because I have a problem not being able to stop eating when I want, I sometimes have to induce vomiting to relieve my stuffed feeling.

#12

(0) 1. I seem to eat just as much when I'm with others (family, social gatherings) as when I'm by myself.
(1) 2. Sometimes, when I'm with other persons, I don't eat as much as I want to eat because I'm self conscious about my eating.
(2) 3. Frequently, I eat only a small amount of food when others are present, because I'm very embarrassed about my eating.
(3) 4. I feel so ashamed about overeating that I pick times to overeat when I know no one will see me. I feel like a "closet eater".

#13

(0) 1. I eat three meals a day with only an occasional between meal snack.
(0) 2. I eat 3 meals a day, but I also normally snack between meals.
(2) 3. When I am snacking heavily, I get in the habit of skipping regular meals.
(3) 4. There are regular periods when I seem to be continually eating, with no planned meals.

#14

(0) 1. I don't think much about trying to control unwanted eating urges.
(1) 2. At least some in the time, I feel my thoughts are pre-occupied with trying to control my eating urges.
(2) 3. I feel that frequently I spend much time thinking about how much I ate or about trying not to eat anymore.
(3) 4. It seems to me that most of my waking hours are pre-occupied by thoughts about eating *or* not eating. I feel like I'm constantly struggling not to eat.

#15

(0) 1. I don't think about food a great deal.
(1) 2. I have strong cravings for food but they last only for brief periods of time.
(2) 3. I have days when I can't seem to think of anything else but food.
(3) 4. Most of my days seem to be pre-occupied with thoughts about food. I feel like I live to eat.

#16

(0) 1. I usually know whether or not I'm physically hungry. I take the right portion of food to satisfy me.
(1) 2. Occasionally, I feel uncertain about knowing whether or not I'm physically hungry. At these times it's hard to know how much food I should take to satisfy me.
(2) 3. Even though I might know how many calories I should eat, I don't have any idea what is a "normal" amount of food for me.

Patient ID: CKD34/HD☐☐☐☐☐☐☐**B**

Date: _____

Added to database ☐

Note. The scoring weights are in parentheses next to each statement. Total scale score is the sum of the weights for the 16 items.

Reference: Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. Addictive Behaviors 1982, 7: 47-55.

Outcome measures data collection
The patient arrives at the study centre and the study conditions checklist is completed on the front page of the data collection form. The data required at each visit will be collected according to the tables attached.

Questionnaires
Patients will be seated and given 2 questionnaires to complete. The Renal QOL - Quality of Life Questionnaire for the research and the HADS (Hospital Anxiety and Depression Scale) as part of the clinical assessment. Code each questionnaire with the patient's individual study ID number and visit code. Patients return the completed questionnaires to the clinic team.

SF-36 QOL
Ask the patient to read each question and circle the answer that most applies to them right now.

HADS – Hospital Anxiety and Depression Scale
Patients are asked to choose one response from the four given for each statement. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

Questionnaire Scoring
Scoring the Renal QOL is completed using a pre-formulated excel spreadsheet.

For the HADS, the questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Add up the total scores for A and D separately.

Clinic blood pressure and heart rate
Ensured that the patient is calm and relaxed.

Allow the patient to rest quietly at a comfortable room temperature for ten minutes before measurements are performed.
The patient will sit quietly with their legs uncrossed and feet flat on the floor.
Measure blood pressure three times at two minute intervals and record all measurements.

For HD patients, predialysis blood pressure is measured according to standard protocol. Also record the last 12 pre-HD blood pressures to calculate average pre HD BP.

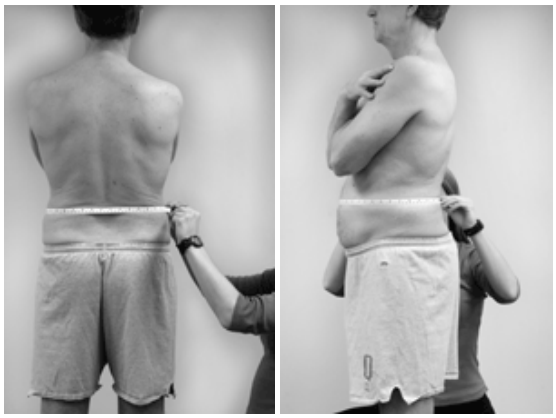
Anthropometry
Height
Using a wall-mounted stadiometer, the patient will be asked to stand upright with heels and shoulders against the measuring rod, knees and back straight and looking forward. The measuring slide will be pushed onto the head so that it is touching without bending. Body height can be obtained from the read-off mark to the nearest whole centimetre.

If the patient is unable to stand, demi-span will be measured to estimate height.

Weight
The scales are placed on a firm, level surface and regularly calibrated. Ask the patient to remove their shoes and any outer clothing, then to step on the platform and remain still; read and record the weight from the display to the nearest 0.1 kg.

Waist and Hip Circumference
For both waist and hip, each measure is taken twice and recorded, if the two readings are > 0.7 cm apart, then further measures should be taken and recorded until two measures are obtained within 0.7 cm of each other.
Protocol for waist and hip circumference measurement:

- Ask the patient to lift any outer clothing clear of the abdomen, but to leave the innermost layer in position. Belts and buttons should be unfastened to release restrictions.
- Ask the patient to stand with their feet shoulder width apart and arms crossed over the chest in a relaxed manner. Kneel on one side of the patient.
- The waist circumference measurement should be taken at the level of the umbilicus. Ask the patient to palpate the abdomen gently to find this landmark, then once located, to return their arms to the crossed position over the chest.
- Position the tape directly around the abdomen so that the inferior edge of the tape is at the level of the land marked point. Use a cross-handed technique to bring the zero line of the tape in line with the measuring aspect of the tape. Ensure that the measuring tape is positioned in a horizontal plane around the abdomen. Apply tension to the tape to ensure it is snug, without causing indentation to the skin.
- At the end of a normal expiration, take the measurement to the nearest 0.1cm.
- The hip circumference measurement should be taken at the widest part of the hips, usually at the greatest protrusion of the buttocks.
- Position the tape directly around the hips, ensuring the tape remains horizontal and parallel to the floor. Use a cross-handed technique to bring the zero line of the tape in line with the measuring aspect of the tape. Apply tension to the tape to ensure it is snug, without causing indentation to the skin.



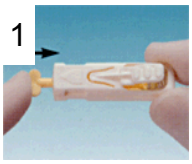
Blood and urine sampling
Urine sampling (CKD 3-4 Study only)
Patients will be asked to provide a 25 ml urine sample in a universal container. The sample is sent to the biochemistry lab with the blood samples.

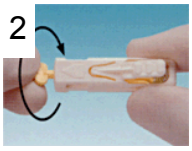
Blood sampling
Patients will be asked to provide a blood sample, taken by a health care assistant, nurse, doctor or qualified phlebotomist.
CKD 3-4 Study: Samples required are 2 x 5ml purple top (EDTA), 4 x 5ml gold top (serum) and 1 x 5 ml grey top (fluoride) vacutainer collection tubes.
HD Study: Samples required are 2 x 5ml purple top (EDTA), 3 x 5ml gold top (serum), 1 x 5 ml grey top (fluoride), and 2 x 10ml large purple (EDTA) vacutainer collection tubes.

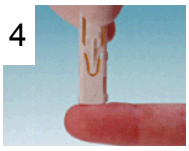
Measurement of Glomerular Filtration Rate using Iohexol Clearance (CKD 3-4 Study only)
Iohexol Clearance Administration Instructions
Administration of iohexol must be performed by a doctor or nurse in an environment with access to resuscitation facilities.

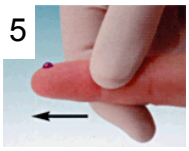
1. Ensure patient has fasted for 12 hours before undertaking the test and has refrained from drinking caffeinated beverages for at least 6 hours
2. Ensure all venous blood samples and baseline fingerprick blood spot are collected before administering iohexol, and leave the butterfly collection set in place
3. Flush the needle with normal saline to ensure patency
4. Administer 5ml of 300mg/ml iohexol solution (Omnipaque 300, Nycomed Amersham Plc, Buckinghamshire, UK) through the collection set and note the exact time on the data collection sheet and blood spot card.
5. Flush the needle with 10ml of 0.9% saline
6. Remove the needle and allow the patient to return to the waiting area to be observed for 15 minutes in case of an adverse reaction

Instructions for fingertip blood sampling prior to and 120, 180 and 240 (or 300) minutes after administration of iohexol (adapted from (Mafham, Niculescu-Duvaz et al. 2007)









1. Arrange equipment (retractable lancet, cotton wool, blood spot card, watch, timer or clock).

2. Wash and dry hands.

3. Prepare retractable lancet (Pictures 1-2).

4. Select sample site. Use the side of the end of one finger (Picture 3).

5. Hold retractable lancet firmly against the sample site and squeeze trigger (Picture 4).

6. Massage finger above sample site until a large droplet has formed (Picture 5).

7. Apply a single large drop to the card surface taking care not to touch the card with the finger. Do not apply several drops to the same card area.

8. Repeat steps 6 and 7 once to collect a second drop onto a separate area of the card.

9. Press the sample site with the cotton wool.
10. Record EXACT time on the card.

11. Allow blood spot card to dry.

12. Return the dried blood spot card to the study clinic using the plastic bag (and stamped addressed envelope provided, if posting.)

Mafham, M. M., I. Niculescu-Duvaz, et al. (2007). "A practical method of measuring glomerular filtration rate by iohexol clearance using dried capillary blood spots." Nephron Clin Pract **106**(3): c104-12.

Measurement of Endothelial Progenitor Cells by Flow Cytometry and Cell Culture
(HD study only)
Samples for endothelial progenitor cell analyses were taken to the laboratory for immediate processing and analysis, performed by the candidate, and the remaining samples, for biochemistry analysis were sent to the Biochemistry Laboratory at King's College Hospital for processing and storage, and were analysed in batches at the end of the study.

Separation of peripheral blood mononuclear cells (PBMC) for endothelial progenitor cell counting and colony-forming unit-Hill (CFU-Hill) colony cell culture
Two x 8 mL samples of peripheral blood collected immediately prior to the start of dialysis, in EDTA coated tubes (BD vacutainer BD: New Jersey), were processed as soon as possible and within two hours of collection.

Procedures for separation of PBMC and preparation of cell cultures were performed in a biological safety cabinet (hood) using aseptic techniques.

Using a Neubauer haemocytometer, nucleated cells were counted using 3% Acetic Acid solution with Methylene Blue at a 1/20 dilution on whole blood (10 µL of blood and 190 µL of Acetic Acid solution).

16 mL of peripheral blood was diluted 1:1 with phosphate buffer solution (PBS) (PAA: Austria), before gently layering 8 mL diluted blood on to each of 4 x 4ml Ficoll-Paque PLUS (StemCell Technologies: France) in 4 x 15ml polypropylene tubes for density gradient centrifugation. The tubes were centrifuged at 300 g, at 24°C for 25 minutes with the brake OFF for extraction of peripheral blood mononuclear cells.

The layer of mononuclear cells between the plasma and the Ficoll-Paque PLUS was collected from each tube with a sterile pipette, and combined in a 50ml polypropylene tube, and washed twice with PBS with 2% FBS Gold fetal bovine serum (PAA: Austria). In the first wash, the final volume was brought to 40 mL with PBS with 2% fetal bovine serum and the tube was centrifuged at 300 g, at 24°C, for 7 minutes with the brake ON to pellet the suspension. The supernatant was removed and the tube tapped to re-suspend the cells, and 6 mL of PBS with 2% fetal bovine serum was added for the second wash. Prior to centrifugation, the sample was re-divided into 4 equal volumes in 4 x 15 mL polypropylene tubes, a further 6 ml of PBS with 2% fetal bovine serum was added to the 50 mL tube, mixed with a pipette to include any remaining cells, then added in 4 equal volumes to the 4 x 15 mL polypropylene tubes. The 4 x 15 mL tubes were spun at 300g for at 24°C, for 7 minutes to complete the second wash.

The supernatant was removed from all four samples and the pellets re-suspended in the residue.

PBMC for endothelial progenitor cell counts
The sample in 1 x 15 mL tube was re-suspended in 1 mL CryoMaxx freezing medium (PAA: Austria) and transferred to a 2 mL CryoTube tube (Nunc: Denmark) for storage at

-80°C, after the nucleated cells were counted using a 1/20 dilution of sample to 3% Acetic Acid with methylene blue (10 µL of sample and 190 µL of Acetic Acid solution). The sample was frozen slowly at 1°C/min in an insulated box at -80°C, and stored at -80°C for later analysis of CD133+, CD34+ and KDR+ cell counts using fluorescence-activated cell sorting (FACS) flow cytometry.

PBMC for CFU-Hill colonies cell culture

The cell culture for formation of CFU-Hill colonies was performed by the candidate according to the procedure outlined in the technical manual, version 3.0.0 (StemCell Technologies: France) [1]. The samples in the other 3 x 15 mL tubes were re-suspended in 1 mL CFU-Hill Liquid Medium in each tube, then all three samples combined into one of the tubes. The nucleated cells were counted using a 1/20 dilution of sample to 3% Acetic Acid with methylene blue (10 µL of sample and 190 µL of Acetic Acid solution). 2 mL/well of CFU-Hill Liquid Medium was added to each of two wells of a 6-well fibronectin coated (BD Biocoat) plate (BD Biosciences: MA, USA), to perform the experiment in duplicate, and 5 x 10^6 cells were plated in each well. The plates were incubated at 37 °C with 95% humidity, 5% CO_2, for two days, to remove mature endothelial cells and some monocytes (Day 0).

After 2 days (Day 2) the non-adherent cells, containing the CFU-Hill colony-forming cells, were collected and cultured for an additional three days to allow for formation of CFU-Hill colonies.

On day 2, the non-adherent cells were collected by gently pipetting the medium up and down three times using a 2 mL pipette. The cells and medium from each well were gently removed with a pipette and placed in separate, labelled, 15 ml polypropylene tubes. The cells in each tube were counted using a 1/10 dilution of Acetic Acid with Methylene Blue (10 µL of sample and 90 µL of Acetic Acid solution). From each well, 1 x 10^6 cells were re-plated, in duplicate, on 24-well fibronectin-coated (BD Biocoat) plates (BD Biosciences; MA, USA), and new CFU-Hill Liquid Medium was added to achieve a final volume of 1.0 mL per well. The plates were incubated at 37 °C with 95% humidity, 5% CO_2 for three days.

On day 5, the medium in each well was gently pipetted up and down three times to suspend the non-adherent cells, and discarded. The wells were gently washed with 1 mL PBS and the PBS was removed. The cell cultures were fixed by gently adding 300 µL of methanol very slowly down the sides of the entire circumference of each well wall, and the plate was incubated, at 37 °C with 95% humidity, and 5% CO_2, for 3 minutes, timed with an electronic timer. The methanol was removed and the cultures were stained with Giemsa Staining Solution (Merck: Germany) diluted 1/20 in distilled water (60 µL of Giesma solution and 1140 µL of distilled water), and incubated for a further 3 minutes. The residual staining solution was removed and the wells were rinsed gently with plain water pipetted into the well and removed, and repeated until the colonies were clearly visible with very little background staining. The plates were stored at room temperature. The absolute numbers of CFU-Hill cell colonies per well were counted using a light microscope. A single CFU-Hill colony was defined as a

central core of round cells surrounded by long, thin, spindle-like cells radiating outwards [2].

Body composition by bioelectrical impedance

The Biospace Inbody 720 analyser will be used.

In HD patients this should be completed on a non HD day. If completed on a HD day, then please note this on the data collection form and continue to collect on HD days for this patient throughout study.

Measurement of body composition by bioelectrical impedance analysis is able to be performed on patients:

- who are able to stand with their arms held away from their body, unaided, for two minutes
- who do not have a pacemaker or metal implant

If able, ask patients to urinate and defecate before undergoing BIA measurement. Request patient to remove outside clothing, empty pockets of heavy items and remove shoes and socks or stockings.

Prior to measurement, the operator should ensure that the results proforma is placed in the printer paper tray, face down, with the heading nearest the outer edge of the tray. Results are printed onto the proforma by the printer attached to the analyser.

- Ask the patient to step onto the 4 cm high platform and place their bare feet slightly apart onto the two footpads which act as electrodes.
- Wipe the hands and feet and electrodes with electrolye coated tissue to ensure good contact. Electrolyte tissue may also need to be placed on top of each foot electrode (not touching each other) to get good contact in patients with thick skin on the soles of their feet.
- Once the patient is still body weight will be recorded. Enter the patient's study ID number including study visit code (B, 3, 6, 9 or 12), age, sex and height (m).
- When the patient is standing comfortably, with their feet placed over the electrodes on the platform, ask them to hold the handgrips (which also act as electrodes) in each hand, and extend their arms straight and away from the body to be clear of their torso.
- Press the Enter key and ask the patient to maintain this position for approximately two minutes, whilst the analysis is performed.

Vascular Stiffness - Pulse Wave Velocity using Vicorder (HD study only)

Set up the laptop and vicorder according to the instruction manual.
Add each new patient as follows
Surname - HD+initials
Forename – study ID
Study ID – study ID

Go to PWV and ensure correct ID is listed and file is saving to HD pilot study file

Brachial to Femoral

- Put cuffs around non fistula arm and top of thigh on same side of body and connect to vicorder, red lead to brachial cuff and blue to femoral cuff
- Measure distance in straight line from top of brachial cuff to top of femoral cuff, record distance
- Press space bar to record PWV, wait 2 cycles and then press space bar, save data and record time and velocity, repeat

Carotid to Femoral

- Remove brachial cuff and place neck band around neck with space for 1-2 fingers inside and connect to vicorder, red lead to neck band and blue to femoral cuff
- Measure distance in straight line from sternal notch to top of femoral cuff, Measure distance from lower edge of carotid band to sternal notch and subtract the distance from the carotid cuff to the sternal notch from the listance between the sternal notch and the femoral cuff
- Enter this distance in the software
- Press space bar to record PWV, wait 2 cycles and then press space bar, save data and record time and velocity, repeat

Measurement of Vascular Stiffness methodology

Vascular (arterial) stiffness was measured with carotid-femoral and brachial-femoral pulse wave velocity (PWV). PWV was measured on an inter-dialysis day of the week using the Vicorder device (Skidmore Medical, United Kingdom), using the oscillometric technique. With the patient lying in a supine position, a blood pressure cuff was placed around the upper thigh and upper arm (brachial-femoral) or a partial cuff placed around the neck at the level of the carotid artery (carotid-femoral). Using a calibrated plastic tape measure, the distance between the top of each cuff (brachial to femoral) or the distance between the sternal notch and the top of the femoral cuff via the umbilicus (carotid-femoral), in a straight line, minus the distance between the lower edge of the carotid cuff to the sternal notch, was measured and entered into the Vicorder software. Both cuffs were inflated simultaneously to 65 mm Hg for 5-10 seconds whilst the carotid and femoral wave-forms were simultaneously recorded and the oscillometric signal from each cuff is digitally analysed to determine the real time pulse delay between the two detected wave-forms. Pulse wave velocity was calculated from the distance measured and the pulse transit time between the two points. Each measurement was performed at least twice and the average velocity recorded. Inter- and intra- tester reliability was measured prior to the study.

Monitoring

Dietary modification

1. Energy and Macronutrient Prescription

Weight Management Programme

Energy requirements for weight loss will be 1400-1800 kcal/day

Protein intake will be optimised for the stage of CKD for each patient, at 1.0 g protein/kg IBW/day for CKD stage 3 and 0.8-1.0g protein/kg IBW/day for CKD stage 4.

Fat intake will be limited to less than 70g per day to minimise the side effects of orlistat.

The remaining kcal will be consumed from carbohydrate sources, with higher fibre choices encouraged when possible.

All patients will be encouraged to modify sodium intake to a "no added salt" diet level, of 80-100 mmol sodium per day. Potassium and phosphate intake will be modified according to serum biochemistry and residual kidney function.

Weight Loss Surgery

Goal energy intake is 1000 kilocalories /day.

Protein intake will be optimised for the stage of CKD for each patient, at 1.0 g protein/kg IBW/day for CKD stage 3, 0.8-1.0g protein/kg IBW/day for CKD stage 4, and 1.2 g protein/kg IBW/day for stage 5 on haemodialysis.

The remaining kcal will be consumed from carbohydrate and fat sources, with low fat choices strongly encouraged. A wide variety of tolerated foods should be eaten.

All patients will be encouraged to modify sodium intake to a "no added salt" diet level, of 80-100 mmol sodium per day. Potassium and phosphate intake will be modified according to serum biochemistry and residual kidney function.

2. Monitoring intake

All study patients

Patients will keep food, fluid and activity diaries for the entire 6 month intervention period. In-depth 3 day food and fluid intake records, followed by dietary assessment interview with the study dietitian will be completed at baseline, 3 months and 6 months during the 6 month intervention period and 3 monthly thereafter, up to 12 months. Patients will be taught how to complete the 3 day food and fluid record using standard household measures to record portions served and plate waste. The study Dietitian will verify the portions using household measures, actual size photographs, product packaging and questioning to verify the record.

Patients consuming >10% more or less kilocalories or protein than prescribed will work with the study Dietitian to adjust intake to meet requirements.

Exercise and Physical Activity

Exercise and physical activity will be monitored using the 3-day food and activity records and direct questioning. Physical activity level will be recorded at 3 monthly intervals. In the Weight Management Programme, formalised testing of exercise parameters is conducted every 3 months.

Subjective Global Assessment

Complete the Subjective Global Assessment with both the medical assessment and physical examination and record the overall rating on the data collection form for each visit.

Post Surgical Complications (weight loss surgery group only)

Record all reported post surgical complications on the data collection form for each study visit. A review of each patient's medical records will be completed periodically throughout

the study to cross check complications from inpatient admissions and post surgical follow up.

Adverse Events
Record all reported adverse events on the data collection form for each study visit.

Appendix E - Information for Participants and Consent Form for The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with chronic kidney disease: a randomised controlled pilot study (Chapter 5)

King's College Hospital NHS Foundation Trust | Guy's and St Thomas' NHS Foundation Trust | King's College London

Information for Participants

Research Ethics Committee Reference Number: 09/H0806/69

Weight Loss in Chronic Kidney Disease Patients with BMI 35-45 kg/m^2

We would like to invite you to participate in this original research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take some time to read and consider the following information carefully and discuss it with friends, relative or your doctor if you want to. Ask us if there is anything that is not clear, or if you would like more information.

Contents

Research Aim - What we would like to find out
This study's purpose is to determine if weight loss can improve kidney function in patients with a body mass index between 35-45 plus chronic kidney disease (CKD). Patients will be randomly allocated to one of two treatments, and followed up over at least 1 year, to find out whether the greater weight loss achieved with surgery improves kidney function and delays progression of chronic kidney disease to end stage when dialysis or a kidney transplant is required.

If you were to participate, you would be allocated by chance to either our established lifestyle-based weight loss programme for 12 months, or to have keyhole surgery to remove two-thirds of your stomach in a procedure called a sleeve gastrectomy, with follow-up for 12 months.

After 12 months, the investigators would like to continue observing patients for another 2 years, with follow up at 2 years and 3 years from the start of the study, to see if there any differences seen between the two treatments are maintained over a longer period of time.

Patients who have already received a kidney transplant are not eligible to participate in this study.

Background Information – What we already know
Over the last 10 years research has shown that obesity is a risk factor for getting chronic kidney disease, even when accounting for high blood pressure and diabetes, the two main causes of chronic kidney disease. Chronic kidney disease and obesity are both high level risk factors for heart disease.

Being overweight or obese may actually damage kidneys by adding pressure to the kidneys, increasing the work done by the kidneys in filtering waste out of the blood and causing small amounts of protein to leak into the urine. Patients with a body mass index of > 35 kg/m2 are not eligible for kidney transplantation and may also be limited in their options for dialysis.

Weight loss surgery is well established as the most effective method of achieving and sustaining long term, significant weight loss. Patients lose an average of 30% of their body weight within 1 year. It is not without risks though, and the bigger you are, the more risky any operation will be. One recent small study suggests that surgery can improve kidney function with weight loss.

Weight loss can also be achieved with our renal weight management programme. The programme uses a combination of low fat eating, exercise and a weight loss medication, called orlistat, and patients lose 5-10% of body weight after 6 months, and this weight loss is sustained up to 2 years. Blood pressure is reduced, exercise capacity improves and patients feel better. About 35% of patients become eligible for kidney transplantation. So far, we have demonstrated stabilisation, but not improvement, in kidney function with this level of weight loss.

There are many hormones and proteins produced by fat cells, the liver and immune cells that circulate around the body. Changes in the levels of these hormones and proteins will occur with weight loss and provide information about the risk of heart and blood vessel disease.

The two treatments

Please remember that you will not be able to choose which treatment you have. You will be put into one group or the other by chance to ensure that patients in both treatment groups are similar at the beginning of the research.

Weight loss programme

The renal weight management clinic has been running at King's College Hospital for 5 years and at Guy's Hospital for 3 years. The weight management programme is an intensive treatment programme including a low fat eating plan, increased activity and exercise with, or without, a weight loss medication called orlistat (or Xenical). When orlistat is taken with meals, it blocks 1/3 of the fat you eat from being absorbed by your body. Orlistat is taken with every meal. Eating fatty foods with orlistat can cause diarrhoea, flatulence or bloating. These side effects are avoided if low fat foods are eaten.

The clinic is run by a specialist Renal Dietitian and Physiotherapist who guide patients to develop their own goals for changing their eating and exercise habits. Patients keep a detailed food and activity diary every month for 6 months. Patients attend the clinic at King's or Guy's hospital once every month for 6 months, and have follow-up visits after 9 months and again at 1 year.

Patients who follow the programme completely and attend all sessions lose an average of 10kg, but many have lost more weight. Patients who do not attend all the sessions tend to lose less weight.

Surgery

Sleeve gastrectomy is a relatively new procedure for weight loss surgery and so far, it has been seen as safe and effective, however there is no information on its success rate after 3 years. It is a restrictive, irreversible, procedure which involves removal of the major portion of the stomach. After a general anaesthetic induces unconsciousness, the surgeon will insert a laparoscope (thin, tube like instrument with a camera to see inside the body) and other slender surgical instruments into the abdominal cavity, through very small surgical cuts through the abdomen. The surgeon will then remove about 2/3 of the stomach after disconnecting its blood supply. This is done with surgical staplers and other instruments. The abdominal wall is then closed with stitches.

The stomach will function as normal, but the reduced size means patients should feel fuller, sooner, so eat less. The level of the hunger hormone, Ghrelin, which is produced in the stomach, will be reduced, and should result in a decreased appetite.

The surgeon may also take a small sample of your fat tissue whilst he is performing the surgery. This tissue will be frozen and stored for later analysis related to this research.

The risks associated with the sleeve gastrectomy are the same as those for any other major abdominal procedure and include haemorrhage (bleeding), leaks from staple lines, anaesthetic and drug reactions, deep vein thrombosis (DVT)/ pulmonary embolus (blood

clots on the lung), infection, marginal ulcer, and lung problems. Overall the risk for any of these early complications varies between 3-7% (or 3-7 in 100) and in experienced hands the risk of death during a sleeve gastrectomy is very low – around 0.1-0.5% (or 1 in 500 to 1 in 1000). There is also a small chance that weight loss will be less than expected. Weight re-gain may occur in 2-3 years if a low fat, low sugar eating plan is not followed in the long term.

After the operation, patients are encouraged to perform exercises to improve lung function and have a test involving swallowing a special fluid to check for leaks in the new stomach, as there is a long staple line in the stomach afterwards. Most patients will stay in hospital for 2-5 days.

Collecting Information
The study team will collect information about participants throughout the study. All data will have patient identifiable information removed (name, address, date of birth) before it is coded and entered into the research database. A separate code breaker file will be kept securely in the study office, to identify patients when new data is added.

The results of the study will be analysed and they may be written up and published in a science journal within two years. If the study finds out something significant the study team may contact the media, and a summary of the results may be published in newspapers. No patient who takes part in the study will be identified in any way in the results.

Telling your GP
The study team will write to your GP to let them know you are participating in this study.

Before you decide to join the study
Patients who are interested in participating in the study will be invited to a pre-assessment appointment with the weight loss surgeon and dietitian. The surgeon will check your medical history and answer all the questions you have about the risks and benefits of surgery. The dietitian will give you information about eating after surgery and about the lifestyle-based weight loss programme.

Tests and measurements during the study
The study involves 7 study visits over 3 years to perform a range of tests, with 5 of these visits in the being completed in the first 12 months of the study. All tests will be done at the beginning, at 6 months and at 12 months after starting the study. Some tests, such as body weight, exercise, blood pressure and blood tests, will be every 3 months, up to 1 year. Only a few tests will be repeated at year 2 and 3 study visits.

Bioelectrical Impedance Analysis
This is a device similar to a pair of scales but instead of measuring only your weight it also measures your body water, muscle and fat levels. You will need to remove your socks and shoes. An undetectable current passes from underneath the feet around the body, measuring the amount of water in the body. Estimates of body fat and lean tissue are then determined. Patients must not eat or drink anything for 2 hours before the test is done. The measurement will be made at baseline and every 3 months up to 1 year.

Blood Tests
Fasting blood samples

The study will involve providing an early morning fasting blood sample at the beginning and every 3 months up to 1 year. Patients will have to attend the hospital in the morning after not eating for 6-12 hours.

Approximately 30 ml of blood will be taken on each occasion. There is a possibility that some bruising may occur on the arm after the sample has been taken.

Some of this blood will be analysed for this study and some samples from this study may be used in future when new techniques are available for measuring previously unknown risk markers.

Blood Pressure
Blood pressure will be measured using an auto upper arm blood pressure monitor when the patient is calm and relaxed, and seated with their legs uncrossed and feet flat on the floor. Blood pressure will be measured three times on one arm with a two minute break between each measurement. The measurement will be made at baseline and every 3 months up to 1 year.

Exercise Tests
Patients will be asked to perform a few simple exercise tests, used routinely in the weight management programme, to measure fitness and muscle strength. Patients only perform to the level they are capable of, and can stop the tests at any time. The tests will be completed every 3 months, up to 1 year.

Flow Mediated Dilatation
An ultrasound scan of the forearm or upper arm is conducted using a blood pressure cuff inflated to reduce blood flow to the forearm, then released. A second scan will be taken after the patient has placed a tablet of glycerol trinitrate (GTN, 25 μg) under their tongue, to open up the blood vessels. Side effects of this medication can include headache and dizziness. The measurement will be made at the beginning, at 6 months and at 1 year.

Food and Activity Diaries
Patients will be required to keep a detailed written record of all food and drink consumed and all activity undertaken for a 3 day period, including 1 weekend day, every 3 months, up to 1 year. The diary will be provided by the study team and can be returned in a pre-stamped pre-addressed envelope provided.

Kidney Function Test
Kidney function will be measured using the iohexol clearance method with finger prick blood sampling. This test takes several hours to complete, but the patient may leave the unit after the initial phase and finish the test elsewhere.

A 4 ml blood sample is taken and the patient will be shown how to perform a self administered fingerprick test and give a sample of two drops of blood onto blotting paper. This is done in exactly the same way someone with diabetes would test their blood sugar.

A small amount of iohexol (5ml) will be slowly injected into a vein in the patient's arm, followed by 10ml of saline. Iohexol is a substance containing iodine, often given to

patients prior to x-rays to highlight a specified area of the body such as the digestive tract or spine, or to test kidney function. Possible side effects of iohexol include headache, nausea or vomiting. The patient will then rest for 15 minutes and be monitored for 45 minutes. Other study measurements may be completed during this time.

Two, three and four or five hours later, the patient will perform a self administered finger prick test using a spring loaded single use safety lancet, to place two separate drops of blood on a strip of blotting paper. Once the strips are dry they can be returned in the pre-stamped, pre-addressed envelope provided. The measurement will be made at the beginning, 6 months, and at 1, 2 and 3 years.

Quality of Life Questionnaire
Patients will be asked to complete the SF-36 Quality of Life questionnaire. This is 12 pre-set questions relating to your own perception of your quality of life. The questionnaire will be completed at the beginning, 6 months, and at 1, 2 and 3 years.

Subjective Global Assessment
This test is used to monitor nutritional status and to detect poor nutrition in patients. It involves answering some general questions about weight change, activity, food intake and gastro-intestinal symptoms, and having a health professional examine your head, shoulders, arms and legs for muscle wasting. You may have to remove some of your clothing so the health professional can see your shoulders, arms, knees and ankles. The measurement will be made at the beginning, at 6 months and at 1 year.

Urine
An early morning urine sample (25ml) will be collected in a standard sample pot at the beginning, at 6 months, and at 1, 2 and 3 years.

Weight, waist and hip circumferences
Body weight will be measured by standing on digital weighing scales in light clothing. Waist and hip circumferences will be measured over light clothing with a soft tape measure. These measurements will be made every 3 months up to 1 year, and again at 2 and 3 years.

It is up to you to decide whether to take part or not
It is up to you to decide whether or not to take part. If you do decide to take part, please keep this information sheet. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

If you do not wish to participate in this study, the study team may ask if you would be prepared to complete some of the tests, and repeat these 6 months and 1 year later, without undertaking any weight loss treatment.

Consent to participate
If you decide to join this study you will be asked to sign a consent form. The consent form will ask that you agree to participate in this study, including random allocation to undergo weight loss surgery or to attend the weight management clinic. The consent form will also ask that you allow your blood, urine and tissue samples to be kept for future research related to this study only.

Who is organising and funding the research?

The study is organised and funded by King's College London and King's College Hospital. Your Doctor, Dietitian and the lead investigator are not being paid to recruit you to this study.

Who has reviewed the study?
This study has been reviewed by the King's College Hospital Research and Development Committee and approved by the London Surrey Borders Research Ethics Committee.

Can I speak to anyone not involved in the study about participating in research?
If you are thinking about participating, and you would like to speak to someone not directly involved with the study, you can contact PALS (the patient advice and liaison service), or the renal anaemia research team to get independent advice about participating in research.

PALS
King's College Hospital tel 020 3299 9000 ext 3601 or visit them on the ground floor, Hambledon Wing 9am to 6pm Monday to Friday

Guy's and St Thomas' Hospital tel 020 7188 8801 or visit them on the second floor, Southwark Wing (Thomas Guy House) 12pm to 3pm Monday to Friday
St George's Hospital tel 020 8725 2453 or visit them in the main corridor between Grosvenor and Lanesborough Wing near the lift foyer 9am to 5pm Monday to Friday
St Helier Hospital tel 020 8296 2508 or visit them on the ground floor next to reception at the main entrance 9am to 5pm Monday to Friday

Or log on to the PALS website
http://www.pals.nhs.uk/

Number of visits

Overall, there are 10 visits to the hospital for the weight management programme treatment and 7 visits to the hospital for the surgery treatment in the first 12 months of the study.

		Weight Management Programme	Weight Loss Surgery
Month Date		Pre assessment Including assessment for surgery and completion of 3 day food and exercise diary	
0		Study visit 1: baseline (beginning) tests	
		Weight management clinic 1st appointment	Surgery – laparoscopic sleeve gastrectomy
1		1 month r/v	Post op surgical review + diet and exercise review
2		2 month r/v	-
3		Study visit 2: 3 month r/v + tests	
4		4 month r/v	-
5		5 month r/v	-
6		Study visit 3: 6 month r/v + tests	
9		Study visit 4: 9 month r/v + tests	
12		Study visit 5: 12 month r/v + tests	
24		Study visit 6: 2 year r/v + tests	
36		Study visit 7: 3 year r/v + tests	

Study Team

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King's College Hospital NHS Foundation Trust

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Consultant Surgeon
King's College Hospital NHS Foundation Trust

Miss Helen MacLaughlin
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Dr Paramit Chowdhury
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Consultant Nephrologist
St Helier Hospital NHS Trust

Dr Iain McPhee
Consultant Nephrologist
St George's Hospital NHS Trust

Professor Tom Sanders
Head of Nutritional Sciences Division
King's College London

Details of local contact

If you require any more information or have any questions, please contact the study co-ordinator:

Helen MacLaughlin
Renal Dietitian
King's College Hospital
020 7848 0431
helen.maclaughlin@kch.nhs.uk

Weight Loss in Chronic Kidney Disease Patients with BMI 35-45 kg/m^2

PARTICIPANT CONSENT FORM

REC Reference Number: 09/H0806/69

Patient identification number for this trial:

Study Title: The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with stages 3-4 chronic kidney disease: a randomised controlled trial

Lead Investigators/Researchers:
Helen MacLaughlin – Renal Dietitian King's College Hospital and PhD candidate King's College London
Dr Iain Macdougall – Consultant Nephrologist King's College Hospital
Mr Ameet Patel – Consultant Surgeon King's College Hospital
Dr Paramit Chowdhury – Consultant Nephrologist Guy's Hospital
Dr Mysore Phanish – Consultant Nephrologist St Helier Hospital
Dr Iain MacPhee – Consultant Nephrologist St George's Hospital
Professor Tom Sanders – Head of Nutritional Sciences Division King's College London

Please initial the boxes

1. I confirm that I have read and understood the information sheet (version 3 November 2009) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that the risks and benefits of participating in the study have been explained to me in a way that I understood. ☐
3. I confirm that the risks and benefits of the individual procedures in the study have been explained to me in a way that I understood. ☐
4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐
5. I understand that responsible individuals from King's College Hospital may look at relevant sections of my medical history. I give permission for these individuals to have access to my records. ☐

10. I agree to take part in the above study, and I understand that I will be allocated a treatment of EITHER diet, exercise and medication for weight loss OR weight loss surgery. I understand that I do not get to choose which treatment I will receive. ☐

11. I agree that the researchers may contact my GP to inform them of my participation in this study. ☐

12. I agree to have blood and urine samples taken for use in this study and to also have samples stored for later research related to this study only. ☐

13. If I am allocated to the surgery treatment, I agree to have a fat tissue biopsy taken at the time of surgery and for the tissue to be stored for later research related to this study only. ☐

Name of Patient_____Date _____
Patient's Signature_____

Name of Researcher _____ Date _____
Researcher's Signature _____

Appendix F - Best Medical Care Weight Management Programme Patient Information (Example) for "The effect of weight loss surgery on preservation of kidney function and cardiovascular disease risk factors in obese patients with chronic kidney disease: a randomised controlled pilot study"

Food Selection Guide 1400 kcal/day eating plan

FOOD GROUP	RECOMMENDED SERVINGS	NUTRIENTS PROVIDED
Bread, **Cereals, Rice,** **Pasta,** **Noodles** 1 serve provides approximately 70 kcal	**4** 1 serve = - 1 slice of bread - ½ medium bread roll - ¼ cup cooked rice - ½ cup cooked pasta or noodles - ½ cup porridge - 2/3 cup (20 g) cereal flakes, or rolled oats - ¼ cup untoasted muesli - < ⅓ cup flour - 1 small (egg sized) potato	These foods are good sources of energy, carbohydrate, protein, dietary fibre and folate. Wholemeal or wholegrain varieties have more fibre, vitamins and minerals.
Vegetables, **legumes**	**2** 1 serve = - 2 heaped tablespoons (80 g or ½ cup) cooked vegetables - ½ cup cooked dried beans, peas or lentils - ¼ tin tomatoes - 1 cup mixed salad, salad leaves	These foods are good sources of vitamins, minerals, dietary fibre and carbohydrate. In particular, Vitamin A, C and folate. Dried beans, peas and lentils are an excellent source of protein.
Fruit	**2** 1 serve = - 1 medium piece (150 g) of fruit (apple, pear, ½ banana, orange) - 2 small pieces (150 g) of fruit (apricot, plum, satsuma) - 1 small handful (10-12) grapes, berries or cherries - 1 cup (150 g) chopped fruit or canned fruit in syrup, drained - 1 tablespoons sultanas - 4 dried apricot halves - 125 mL fruit juice	These are a good source of Vitamin C and folate, carbohydrate and fibre, especially in the edible skins. Juices have much lower fibre content and are high in potassium.

Milk, yoghurt, cheese	**2** 1 serve = - ½ cup (125 ml) semi skimmed milk / soy milk (calcium enriched) - 1 slice (20 g) cheese - 1 small tub (125 g) low fat yogurt - ½ cup (125 ml) low fat custard	Dairy foods are good sources of calcium, protein, riboflavin and vitamin B12. Choosing the low fat varieties will reduce your calories eaten and reduce your saturated fat intake.
Meat, fish, poultry, eggs, nuts, legumes	**3-4** 1 serve = - 65-100g cooked lean beef, lamb, pork, chicken or turkey (eg ½ cup lean mince, 2 small chops, 2 slices roast meat, 1 chicken thigh or small breast) - ¾ cup cooked dhal, lentils, chick peas, kidney beans, other dried beans and peas - 80-120 g cooked fish - 2 small eggs - ⅓ cup almonds - 1 tablespoon seeds - 100-150g Quorn or tofu	These are good sources of protein, iron, niacin and vitamin B12. Trimming all meats or visible fat will reduce the energy content.
Water	1 serve = 125 ml glass or cup - water - tea and coffee - diet squash and fizzy drinks - soup - ice cubes	Keep within your fluid allowance each day
Extras 1 serve provides approximately 70 kcal	0- 2 1 serve = - 2 tsp oil or margarine - 1 mini bar or 3 squares chocolate - 10 rice crackers or mini rice cakes; 2 ryvita, 2 cream crackers - 2 plain biscuits - 1 cup popcorn - 100 ml wine, 375ml light or 250 ml regular beer - 2 small scoops ice cream	These foods are not essential to provide nutrients the body needs and many contain too much fat, salt and sugar.

SAMPLE MEAL PLAN

1400 kcal/day eating plan

BREAKFAST	2 slices of toast with a thin scrape of margarine or jam Plus low fat yoghurt (125g) and 1 small banana Bowl of cereal and ½ cup of semi-skimmed milk with ½ banana or ½ grated apple Rolled oats with ½ cup milk (+ water), 1 tablespoon raisins, 1 tablespoon seeds and ½ grated apple 2 eggs (scrambled/omelette/poached) + beans & tomatoes + 1 slice toast
LUNCH	Toasted cheese and tomato sandwich Salad with tuna (80g), egg, tomato, cucumber, green beans, olives with low calorie salad dressing Sandwich/ bread roll/ pita bread with 60g lean ham/tuna/chicken/turkey/beef/egg with salad (add mustard, cranberry sauce or low fat mayo) Tuna or salmon pasta or couscous salad with peppers and sweet corn with low fat mayo or oil free dressing Jacket potato with reduced fat spread and baked beans 100g ham/prawns/salmon with greek salad (tomato, feta cheese, cucumber, spring onion, olives, 2 teaspoons olive oil/vinegar) with 4 rye or wheat crackers PLUS apple/pear/2 satsumas/12 grapes
DINNER	200g lean meat/ chicken/ fish/ lamb/ pork with 1 cup boiled vegetables Omelette (2 eggs, with 40g cheese, peppers and spring onions) 150g meat/fish/lentil and vegetable curry with low fat yogurt or light coconut milk, with 2/3 cup cooked rice 1 cup meat/veg stew with 2 small pieces of plantain, yam or sweet potato PLUS 125g low fat yoghurt, 2 small scoops reduced fat ice cream or frozen yogurt or 200g reduced fat rice pudding

Keeping track of your meals and activity

Your Meal and Activity Plan	**Checklist**
Breakfast  	Use this checklist to keep track of your physical activity and how many serves you have from each food group each day. Record activity in blocks of 10 minutes and 30 minutes each day is the minimum recommended for adults Breads, cereals, rice pasta, noodles ☐ ☐ ☐ ☐ Vegetables, legumes ☐ ☐ Fruit ☐ ☐ Milk, yoghurt, cheese ☐ ☐ Meat, fish, poultry, eggs, nuts, legumes ☐ ☐ ☐ ☐ Water ☐ ☐ ☐ ☐ ☐ Extras ☐ ☐ Physical activity (per 10 mins) ☐ ☐ ☐ ☐
Mid-morning 	
Lunch  	
Mid-afternoon 	
Dinner  	
Extras  	
Notes	